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EXPERIMENTAL DISSEMINATED ENCEPHALOPATHY IN THE MONKEY

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It has recently been shown that injection of suspensions or extracts of brain tissue may produce an experimental type of encephalopathy bearing certain similarities to forms observed in the human being. In 1925 Koritschoner and Schweinburg,[1] and in 1932 Hurst,[2] obtained paralysis in rabbits after injections of human brain tissue. However, these investigators were unable to demonstrate pathologic changes in the nervous system of the affected animals. After these experiments, Rivers, Sprunt and Berry [3] and Rivers and Schwentker,[4] by repeated intramuscular injections of aqueous emulsions and alcohol-ether extracts of sterile normal rabbit brains, produced in monkeys a type of "encephalomyelitis" accompanied by destruction of myelin. Signs of disseminated lesions of the central nervous system became manifest after injections had been continued for several months. The pathologic changes consisted of areas of demyelination scattered throughout the central nervous system. These were perivascular and contained a variety of cellular elements, including fatty granular cells, leukocytes and giant cells.

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1. Koritschoner, R., and Schweinburg, F.: Klinische und experimentelle Beobachtungen über Lähmungen nach Wutschutzimpfung, Ztschr. f. Immunitätsforsch. u. exper. Therap. **42**:217, 1925.

2. Hurst, E. W.: The Effects of the Injection of Normal Brain Emulsion into Rabbits, J. Hyg. **32**:33, 1932.

3. Rivers, T. M.; Sprunt, D. H., and Berry, G. P.: Observations on Attempts to Produce Acute Disseminated Encephalomyelitis in Monkeys, J. Exper. Med. **58**: 39, 1933.

4. Rivers, T. M., and Schwentker, F. F.: Encephalomyelitis Accompanied by Myelin Destruction Experimentally Produced in Monkeys, J. Exper. Med. **61**:689, 1935.

The importance of these experiments warranted their repetition and extension. It is the purpose of the present paper to report the pathologic changes in a first series of experiments and to comment on the significance of these observations in relation to the pathogenesis of both the experimental type of encephalitis and the similar forms observed in man.

METHODS AND MATERIAL

The material for injection consisted of a fresh aqueous emulsion and an alcohol and ether extract of rabbit brain. These were prepared according to the directions given by Rivers and Schwentker.[4] To prepare the fresh aqueous emulsion, 1 normal rabbit brain was ground in a mortar, 40 cc. of physiologic solution of sodium chloride and 10 cc. of 95 per cent alcohol were added, and the emulsion was centrifuged at low speed for a few minutes. Only the supernatant material was used for injection. The alcohol-ether extract was prepared as follows: The brains of 2 rabbits were ground in a mortar and successively extracted for five days at 37 C. with 150 cc. of absolute alcohol and 150 cc. of ether. The combined ether and alcohol extracts were reduced to about 70 cc. *in vacuo*.

The injections were given intramuscularly, approximately twice a week. The dose was that reported by Rivers and Schwentker, i. e., 4 cc. of the fresh suspension and 1 cc. of the alcohol-ether extract. The latter was mixed with 4 cc. of physiologic solution of sodium chloride. Instead of alternating regularly the alcohol-ether extract and the equeous emulsion, three injections of the former were given in succession, followed by three injections of the latter.

Data on Seven Monkeys Given Inoculations of Rabbit Brain

Monkey No.	Duration, Days	No. of Injections
663	112	29
673	126	31
667	154	40
677	178	45
676	299	76
722	374	89
696	405	103

All monkeys (Macacus rhesus) were healthy and half grown. They were housed in the same room with and received the same food as numerous other monkeys which were used as controls.

Autopsies were performed immediately after death. Sections from different parts of the central nervous system were stained by a variety of methods. These included: hematoxylin and eosin for cells; the Van Gieson, Mallory and Masson stains for cells and connective tissue; the Klarfeld method for connective tissue; the Nissl stain for neuron cells; the Spielmeyer and Weil methods for myelin; the Bielschowsky method for axis-cylinders; the Holzer, Cajal and Hortega methods for glia; scarlet red, sudan III, and sudan black for fatty substances; the Giemsa and Unna methods for blood elements and Weigert's stain for fibrin. Particular care was taken, whenever possible, to study serial sections, staining each consecutive section by a different method.

EXPERIMENTS

Seven monkeys were given inoculations for a period varying from one hundred and twelve to four hundred and five days, the number of inoculations ranging from twenty-nine to one hundred and three.

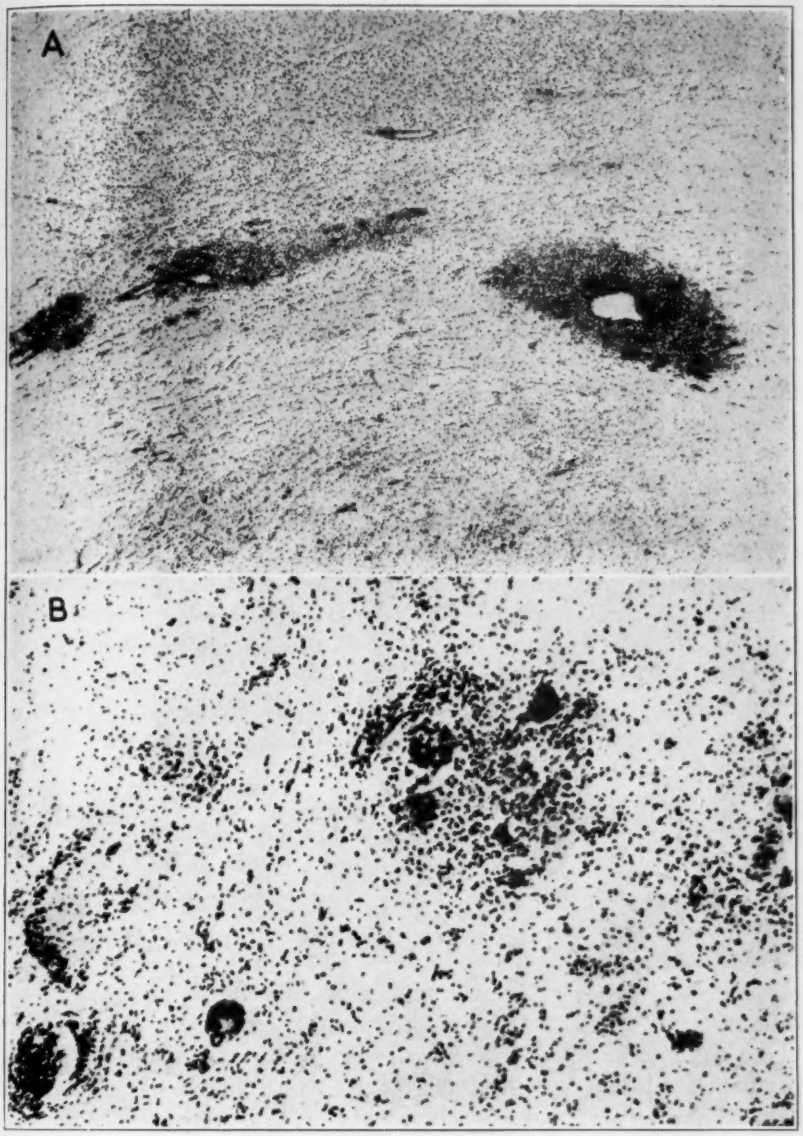

Fig. 1.—*A*, typical lesions in the white matter of the brain; low power. *B*, lesion in the white matter of the pons; medium power. Note the numerous giant cells. Nissl stain.

RESULTS

As the clinical course and the pathologic changes in the different animals were similar, a general description will be given.

Clinical Signs.—Evidences of involvement of the nervous system were observed in all animals, with the exception of monkey 722. This animal showed only occasional nystagmus. Neurologic signs appeared after a minimum of one hundred days. Forced position of the head, ataxia, coarse tremors, nystagmus, ptosis of the eyelids and spastic paresis were the most frequent symptoms encountered. An examination of the spinal fluid was not made. The course of the condition, once the neurologic symptoms became manifest, was progressive; its duration varied from twelve to ninety days. The injections were continued after the occurrence of neurologic signs until it was apparent that the animal would not live much longer; the animals were then killed. Two monkeys died spontaneously.

Pathologic Changes.—The pathologic picture in all animals consisted mainly of circumscribed lesions disseminated throughout the central nervous system. As shown with cell stains, the lesion consisted of an accumulation of cellular elements. Characteristic lesions were generally observed in the white matter. The centrum ovale (fig. 1 *A*) and the white substance of the cerebellum and pons (fig. 1 *B*) were chiefly involved. No preference was observed for the periventricular regions. In 1 case several foci were observed in the subcortical white matter, where the lesion often impinged on the adjacent gray matter, and in another case a well circumscribed lesion was seen in the optic tract. There were a few small foci in the gray matter of the cortex and the basal ganglia.

In the central part of a characteristic lesion there was a blood vessel, usually a small vein; when this was not shown in one section, successive serial sections often revealed the presence of a blood vessel within the lesion. Therefore, the perivascular character of the typical lesion was generally discernible. Although perivascular, the lesion spread fairly widely outward from the vessel walls.

Study of the perivascular accumulation of cells permitted its classification under three main types; in the first, which was the most frequently encountered, the cellular content consisted exclusively of compound granular elements (fig. 2). These, in Nissl preparations, showed the well known features of abundant, foamy cytoplasm with an eccentric, small nucleus, and in Herxheimer preparations, the characteristic red color. In the second type (fig. 2 *B*), which was rarely seen, the cellular infiltration did not contain gitter cells, but consisted of lymphocytes, plasma cells and polymorphonuclear elements. Several of the cells last mentioned appeared to be eosinophilic. Finally, in a third

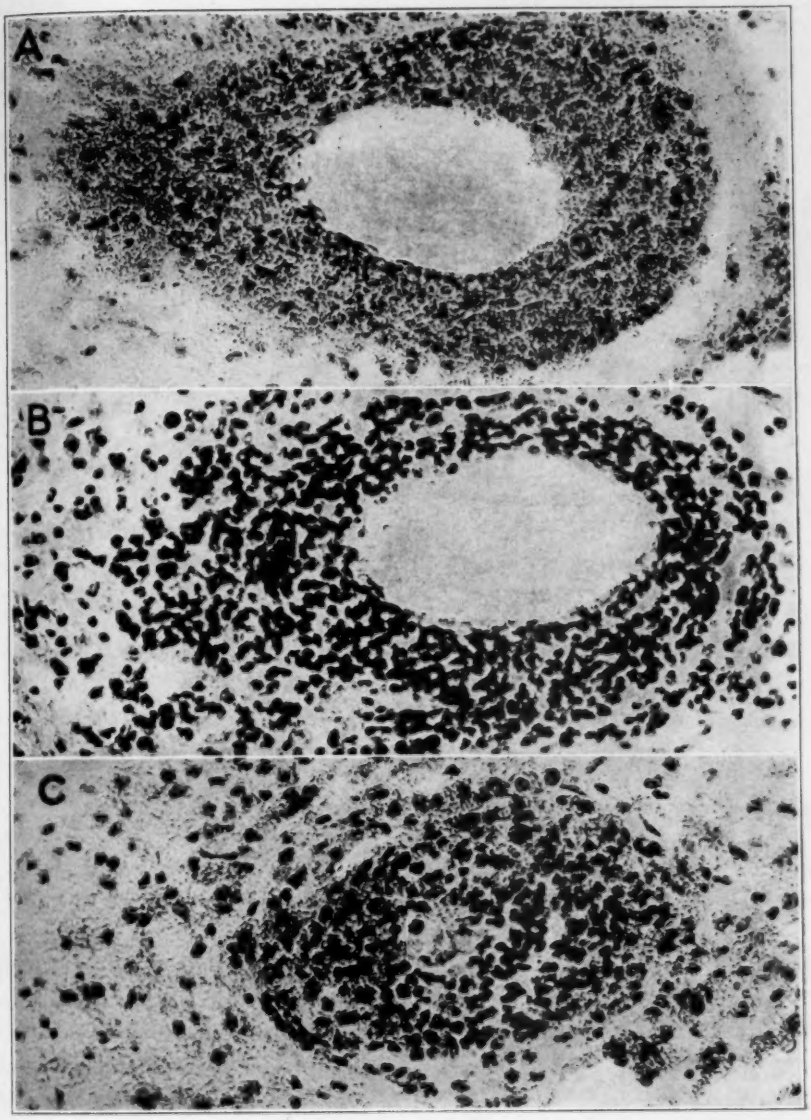

Fig. 2.—Perivascular infiltration. *A*, compound granular elements exclusively; *B*, hematogenous elements exclusively; and *C*, compound granular corpuscles and hematogenous cells. Herxheimer stain; high power.

type (fig. 2 *C*), both gitter and hematogenous cells were observed, the latter being generally in the center, within the perivascular space, the former at the periphery.

One of the most striking features of the pathologic picture was the presence among the cellular elements of a large number of giant cells, which showed numerous nuclei (figs. 1 *B* and 3). Giant cells were not present in all areas of cellular proliferation and seemed generally to be more numerous in areas more severely involved. The cytoplasm of such cells appeared foamy in Nissl preparations and contained granules which stained bright red with scarlet red; the nuclei were similar to

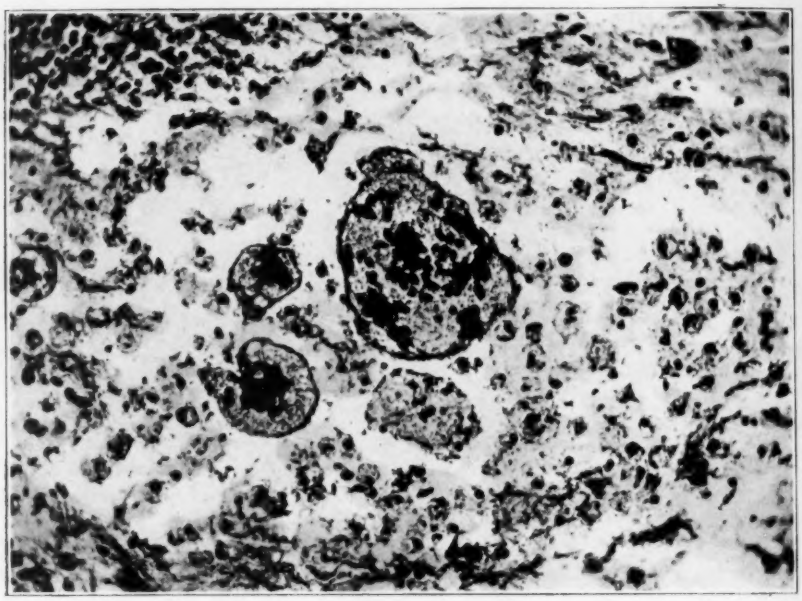

Fig. 3.—Giant cells. Hematoxylin and eosin stain; high power.

those of gitter cells. On many occasions pictures were observed which could be interpreted as phases of fusion representing transitions from a cluster of individual gitter cells to a giant cell. Occasionally, a second type of giant cells could be distinguished in which the cytoplasm was homogeneous and contained no fatlike substances stainable with scarlet red. The nuclei as shown with the Nissl stain bore similarities to the macroglia nuclei, being large and pale, with few granules of chromatin.

In myelin preparations (Weigert, Spielmeyer, Weil) areas of destruction of the myelin sheaths, round or oval, were observed to be a part of the lesions (fig. 4). In the center the destruction of myelin was complete, no fragments being discernible. At the periphery a tran-

sitional zone was often observed, characterized by swelling, beadlike appearance and fragmentation of the myelin sheaths. This zone, however, was generally limited, so that the transition between destroyed and normal myelin was rather abrupt, the demyelinated area being sharply defined.

In Bielschowsky preparations, a large number of axis-cylinders were destroyed. The few remaining showed irregular swellings and a corkscrew appearance. The destruction was less marked as one passed from the center to the periphery of the lesion.

Generally, in Cajal and Holzer preparations the neuroglia in the central portion of the lesion appeared to be almost completely lacking

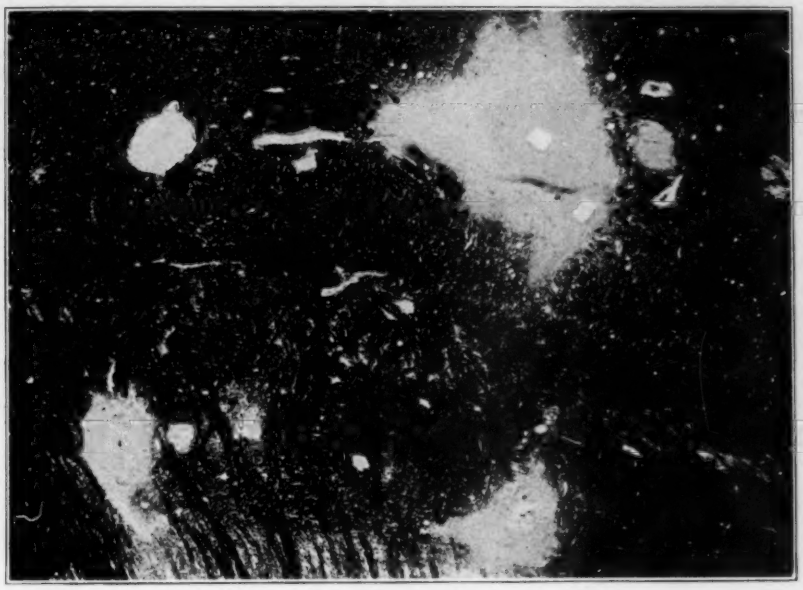

Fig. 4.—Circumscribed areas of demyelination in the Spielmeyer preparation. Low power.

(fig. 5); at the periphery degenerated forms could be seen, their cytoplasm being swollen and their dendrites broken down. In the normal tissue adjacent to the lesion the neuroglia showed definite signs of progressive reaction. However, on several occasions destructive and degenerative alterations were absent, and hyperplasic and hypertrophic changes predominated within the lesion, resulting in a well circumscribed patch of proliferating glia cells with numerous interwoven fibrils (fig. 6).

Hortega preparations showed a conspicuous increase of microglia cells; in the center of the lesion most of the microgliacytes were transformed into compound granular cells, which made up the totality or

the majority of the cellular elements present within the lesion. At the periphery various phases of transformation of the microgliacytes into compound granular cells could be observed. The cytoplasmic content of the gitter cells stained bright red with scarlet red and sudan III and deep black with sudan black.

In Klarfeld preparations some foci showed an appreciable increase of connective tissue, which appeared as coarse fibers seemingly originating from the vessel walls.

There was no evidence of partial or complete obliteration of the lumen of the blood vessels in any of the lesions. Particular attention

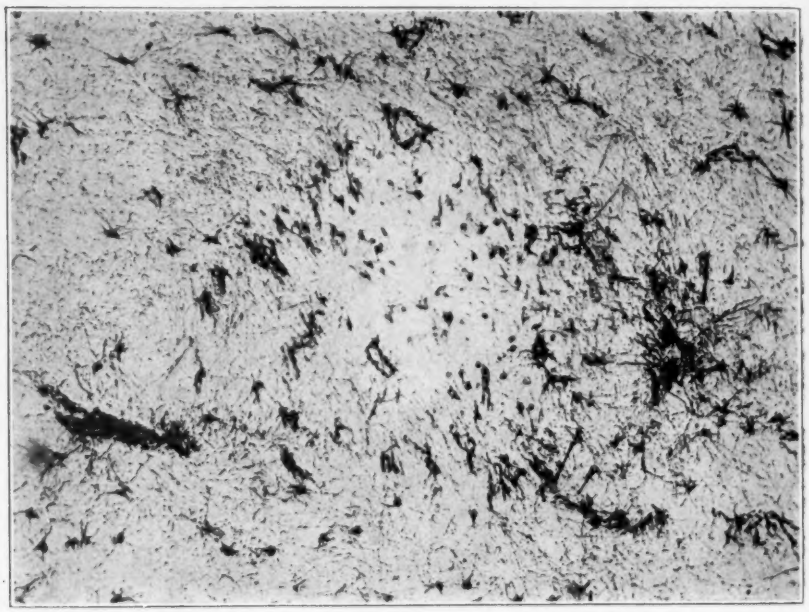

Fig. 5.—Typical lesions in the Cajal preparation, showing disappearance of neuroglia in the center and hypertrophy at the periphery.

was paid to a search for thrombi; Masson's and Mallory's stains were used, in addition to the Weigert method for fibrin. There were no clumping of platelets, threads of fibrin or entangled leukocytes within the lesion. Organization by connective tissue or canalization of thrombi was likewise absent. The blood vessels contained red cells, which in only a few instances appeared somewhat conglutinated. Congestion was often observed, but there were no hemorrhages. In 2 cases methods of staining thrombi were applied to other viscera, including the liver, kidney, heart and lung, with negative results.

In addition to characteristic circumscribed lesions, larger foci were seen, particularly in 2 cases. The fundamental histologic features were

the same, i. e., destruction of myelin and formation of numerous gitter cells. However, the lesions extended over a larger area; in 1 case almost the entire white matter of the cerebellum appeared involved. The perivascular cellular proliferation was made up of gitter cells and hematogenous elements; the last were more numerous than in the small foci. The large areas of demyelination were irregular. It appeared obvious in our material that a large focus had resulted from the confluence of several small perivascular foci.

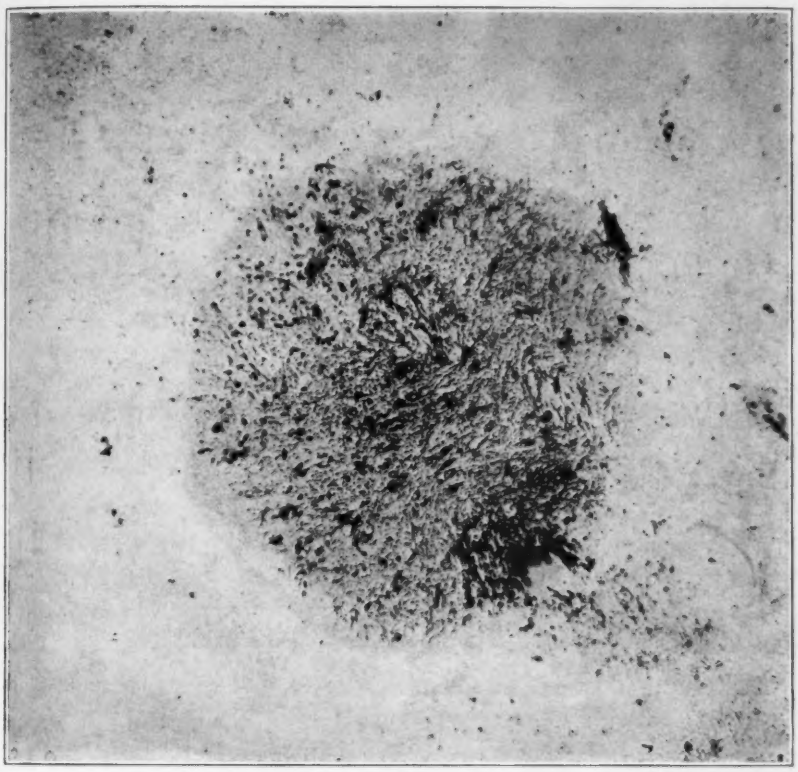

Fig. 6.—Circumscribed patch of proliferating glia. Holzer stain; low power.

Other atypical lesions of demyelination were observed in 2 cases. They consisted of large patches of partial breaking down of myelin sheaths (fig. 7). These showed partial fragmentation, localized swelling and a beadlike appearance. No apparent connection with blood vessels could be observed in these cases. In the region where this type of demyelination was observed macroglia showed progressive changes, diffusely distributed over a large area.

Often, another type of lesion was observed, which could be interpreted as the first stage in the formation of a typical focus. It consisted of mobilization of microgliacytes along a small blood vessel. These cells, which were seen to gather in three or four concentric or parallel rows in the vicinity of a vessel, showed signs of pathologic change, being swollen and larger than normal and having lost most of their dendrites, on their way to transformation into compound granular cells. However, in Hortega preparations counterstained with scarlet red, little or no fat was apparent in their cytoplasm. In the same regions the myelin sheaths appeared occasionally irregularly swollen and partially fragmented. Although no direct evidence can be produced, it is believed that mobilization of microglia and swelling of the myelin sheaths are two aspects of the same incipient pathologic process.

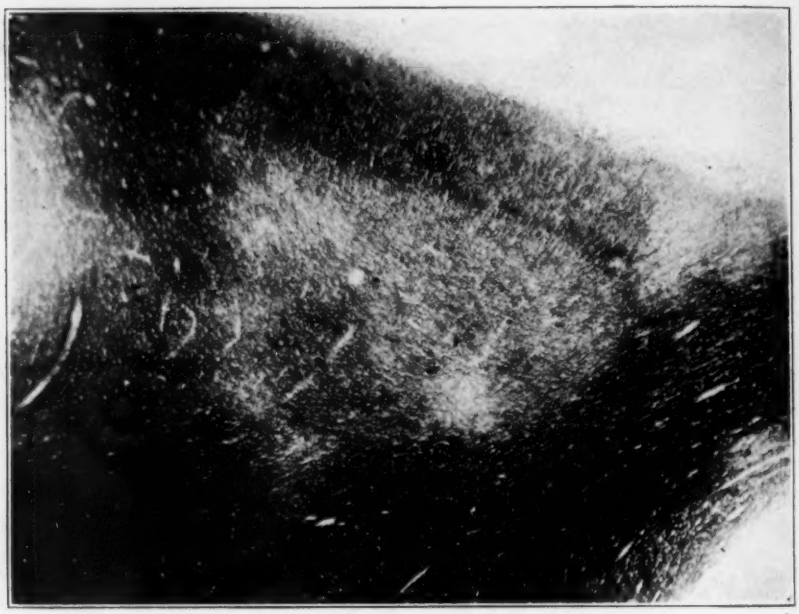

Fig. 7.—Diffuse partial demyelination in the white matter. Spielmeyer stain; low power.

COMMENT

The main histologic features of the lesions just described fit well into the group of so-called multiple degenerative softenings. With this name Hassin [5] described a specific pathologic group characterized by "simultaneous destruction of the myelin and the axons, the prevalence

5. Hassin, G. B.: Pathologic Features of Multiple Sclerosis and Allied Conditions, Arch. Neurol. & Psychiat. **38**:713 (Oct.) 1937.

of the microglial reaction and the vast extra-adventitial destruction of the nerve parenchyma," with rapid and destructive course. "Multiple degenerative softenings" show, in Hassin's estimation, essential differences from vascular softenings and lesions of multiple sclerosis, the last being characterized by "widespread primary swelling and breaking down of myelin, proliferation of oligoglia and astrocytes, giving rise to a variety of phagocytic formations, followed by dense glial sclerosis." Without entering into a discussion of Hassin's conception of a separate clinicopathologic group disclosing "degenerative softenings," we wish to point out only that there are doubtless instances in which characteristic foci of "multiple degenerative softening" are found together with patches of typical multiple sclerosis (Pette,[6] Juba[7]), thus indicating occasionally a probable common origin. In the present material, also, patches of sclerosis were occasionally observed, as illustrated by figure 6. To be sure, the problem of the relationship between multiple sclerosis and "multiple degenerative softenings" is still unsettled and requires more investigation; it is hoped that data may be offered by the study, now in progress, of a new series of animals kept alive for the chronic stages of this experimental condition.

The similarity of the lesions described to those observed in "exanthematic encephalitis" is close enough to warrant comment. The descriptions of pathologic changes in various forms of "encephalitides" which occasionally follow vaccinia or exanthematic diseases of childhood and of those in certain cases of so-called acute multiple sclerosis leave little doubt as to the close pathologic similarities of these conditions. The pathologic picture consists of disseminated perivascular lesions in which the myelin, and to a lesser extent the axis-cylinders, are destroyed and the macroglia is degenerated. The lesion, which is situated mainly in the white matter, is filled with elements of the microglial type undergoing transformation into gitter cells. Generally, a few hematogenous cells are also seen. The etiologic factors in these conditions remain obscure. Several theories have been advanced, but no convincing evidence has yet been produced in favor of any of them.

Because of the marked similarity between the lesion just described in monkeys and that in "exanthematic encephalitis," it might reasonably be expected that an investigation of the mechanism operating in the former would give a clue to the solution of the cause of the latter.

In an attempt to clarify the pathogenesis of the experimental lesions described, a few possible mechanisms will be briefly discussed.

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6. Pette, H.: Ueber die Pathogenese der multiplen Sklerose, Deutsche Ztschr. f. Nervenh. **105**:76, 1928.

7. Juba, A.: Die Beziehungen zwischen multipler Sklerose und Encephalomyelitis disseminata, Deutsche Ztschr. f. Nervenh. **143**:268, 1937.

1. *Embolism.*—Although particular care was taken to perform the injection subcutaneously, the possibility of fat embolism should be ruled out. This hypothesis is not consistent with the actual pathologic observation. The pathologic picture of multiple embolic softenings consists of disseminated foci which are made up predominantly of hematogenous cells mixed with gitter cells. The vessels are generally altered. Small hemorrhages are frequent. The gray matter is much more affected than the white (Neubürger,[8] Weimann,[9] Müller[10]). Liquefaction of the nerve parenchyma takes place, and organization of the lesion is carried on mainly by connective tissue. Moreover, the cortex shows characteristic cytoarchitectual alterations consisting of local loss of nerve cells; ischemic changes of individual cells are observed. In our cases, the foci were almost exclusively in the white matter; hematogenous cells were only occasionally present, and no hemorrhages or cortical cellular ischemic changes were observed. Moreover, in no case was there seen a fat embolus within the lumen of a blood vessel or alterations of the vessel walls.

2. *Thrombosis.*—This possibility should be especially considered in view of the recent claims of Putnam[11] and his collaborators that encephalomyelitis may be produced by thrombi of small vessels of the brain. It has long been known (Kusama,[12] Fellner[13]) that extracts of organs when injected intravenously cause general intravascular clotting. Moreover, Hoefer, Putnam and Gray[14] observed that Rivers' extracts have coagulant properties when given intravenously; they failed, however, to observe lesions in the brain after administration of these extracts.

Histologic features have been repeatedly described with a view to differentiation of thrombotic softenings; these foci are entirely devoid of structure, and infiltration is primarily with hematogenous elements, the microglia partaking only in a later stage; hemorrhages are

8. Neubürger, K.: Ueber cerebrale Fett- und Luftembolie, Ztschr. f. d. ges. Neurol. u. Psychiat. **95**:278, 1925.

9. Weimann, W.: Besondere Hirnbefunde bei cerebraler Fettembolie, Ztschr. f. d. ges. Neurol. u. Psychiat. **120**:68, 1929.

10. Müller, G.: Zur Frage der Altersbestimmung histologischer Veränderungen, Ztschr. f. d. ges. Neurol. u. Psychiat. **124**:1, 1930.

11. Putnam, T. J.: Evidences of Vascular Occlusion in Multiple Sclerosis and "Encephalomyelitis," Arch. Neurol. & Psychiat. **37**:1298 (June) 1937.

12. Kusama, S.: Ueber Aufbau und Entstehung der toxischen Thrombose und deren Bedeutung, Beitr. z. path. Anat. u. z. allg. Path. **55**:459, 1913.

13. Fellner, O. O.: Thrombose und innere Sekretion? München. med. Wchnschr. **59**:537, 1912.

14. Hoefer, P. F. A.; Putnam, T. J., and Gray, M. G.: Experimental "Encephalitis" Produced by Intravenous Injection of Various Coagulants, Arch. Neurol. & Psychiat. **39**:799 (April) 1938.

frequent and the vessel walls deeply altered; the neuron cells are early damaged by anoxia brought about by vascular obstruction. It seems from our study that many of these features were lacking. It appears, however, that the best criterion for disposing of the question is the actual demonstration of thrombi in the blood vessels about which the lesion is centered, rather than on the minute histopathologic features of the lesion. In our preparations there were not observed in the brain any typical thrombi or features, such as clumping of platelets or threads of fibrin, which are considered to be an integral part of every thrombus (Johnson [15]). Late stages of thrombosis, such as organization with connective tissue, were likewise absent. In addition, thrombi were not observed in other organs. There is therefore enough evidence for excluding thrombosis as the cause of the cerebral lesions. It should be noted that in the recent experiments of Hoefer, Putnam and Gray,[14] as well as in the old experiments of Fellner,[13] the organ extracts were given intravenously and generalized thrombosis was observed immediately, whereas in our cases subcutaneous injections were given and the first symptoms appeared after several months.

3. *Neurotoxin.*—The hypothesis that antibodies specific for a given organ are responsible for certain diseases of unknown etiology has been brought forward many times, but little evidence has been produced that organ-specific antigens actually occur. However, as far as the central nervous system is concerned, recent experiments (Witebsky and Steinfeld,[16] Lewis,[17] Schwentker and Rivers [18]) have demonstrated that emulsions of heterologous brain tissue when repeatedly injected into rabbits are capable of inciting antibodies specific for the rabbit brain. The antibodies can be demonstrated either by complement fixation tests or by precipitin reactions. Further, brain-specific antibodies are also produced by an alcohol extract of brain provided an antigenically active protein is added. The reacting antigen appears to be a lipoid functioning as a haptene, which is actuated by a protein. It will be noted that in the present experiments a lipoid substance was contained in both the emulsion and the ether-alcohol extract, and a protein was doubtless present in the emulsion. There is, therefore, enough justification for

15. Johnson, W. R.: Experimental Thrombosis, Folia haemat. **48**:473, 1932.

16. Witebsky, E., and Steinfeld, J.: Untersuchungen über spezifische Antigenfunktionen von Organen, Ztschr. f. Immunitätsforsch. u. exper. Therap. **58**:271, 1928.

17. Lewis, J. H.: The Immunologic Specificity of Brain Tissue, J. Immunol. **24**:193, 1933.

18. Schwentker, F. F., and Rivers, T. M.: The Antibody Response of Rabbits to Injections of Emulsion and Extracts of Homologous Brain, J. Exper. Med. **60**:559, 1934.

assuming that the lesions in the brain may be associated with the development of antibodies specific for brain. More evidence is expected from experiments, now in progress in our department, aiming to incite brain antibodies under various conditions.

It will be noted that during antirabies treatment, in which a heterologous brain emulsion is repeatedly injected, conditions almost identical with the present experiments occur. The encephalomyelitis which occasionally results shows pathologic features (Bassoe and Grinker [19]) similar to those described in the present experimental type. There seems to be little difficulty, therefore, in assuming a similar mechanism of production.

It is more difficult to extend such an explanation to cases of postexanthematic encephalitides, in which no heterologous brain tissue is injected. However, experiments of Schwentker and Rivers [18] have proved that homologous brain altered by autolysis or by infection with vaccine virus becomes antigenic and is then capable of inducing the production of antibodies specific for brain tissue. One may speculate on the possibility that invasion of the central nervous system by a virus may occasionally result in the formation of brain antibodies and the subsequent development of encephalopathy.

SUMMARY

Seven monkeys were given inoculations for a period varying from four to thirteen months with sterile extract and emulsion of rabbit brain. A progressive condition, characterized by symptoms of widespread involvement of the central nervous system, developed.

Pathologic examination showed disseminated perivascular lesions characterized by destruction of myelin and accumulations of fatty granular cells. The macroglia at times had degenerated, and at other times showed proliferative changes. In addition, large areas of partial demyelination which showed no apparent relation to blood vessels were observed.

The pathogenesis of this experimental encephalopathy is investigated, and its significance is briefly discussed in relation to similar conditions in man.

Miss Margaret Mara gave technical assistance.

DISCUSSION

DR. BEN H. BALSER, New York: My colleagues and I have been carrying on similar experiments, first, at the Montefiore Hospital and, since the beginning of this year, at the Mount Sinai Hospital. In our work we have used sterile human

19. Bassoe, P., and Grinker, R. R.: Human Rabies and Rabies Vaccine Encephalomyelitis: A Clinicopathologic Study, Arch. Neurol. & Psychiat. **23**: 1138 (June) 1930.

brain material obtained shortly after death and prepared as a 5 per cent suspension in Locke's solution. Five cubic centimeters of this suspension was introduced intramuscularly into Macacus rhesus monkeys. One of the animals so treated presented, after the fifty-fourth injection, rapidly advancing and severe ataxia, accompanied by generalized paresis and followed by blindness and deafness. This animal received eight more injections of the suspension and then was killed. The brain and spinal cord were immediately placed in solution of formaldehyde U. S. P. and submitted to Dr. J. H. Globus for histologic studies.

A large amount of fat was noted in the dorsal column of the spinal cord, almost throughout its length. Less massive and somewhat scattered accumulations of fat were observed in the subcortex and the zone surrounding the lateral ventricles. This accumulation of fat was most marked in the occipital lobe, and was restricted to the areas mentioned. A corresponding increase in glial elements and alterations in the myelin sheaths were observed in the same areas. The pathologic picture bore a strong resemblance to that of disseminated sclerosis. Contrary to the observations reported by Dr. Ferraro and Dr. Jervis, accumulations of fat in our material lacked the perivascular arrangement which they described.

We are also studying the presence and the fluctuation of a "brain-specific antibody response," but as yet we have been unable to reach any conclusions with regard to these experiments.

Dr. G. A. Jervis, New York: In answer to Dr. Balser, we also found diffuse areas of demyelination in which no apparent relationship to blood vessels could be observed. One of the slides just shown is an instance. However, only in 1 monkey was this marked. The problem of formation of brain-specific antibodies seems to me important. Experiments are now in progress to induce production of brain antibodies under different conditions. I hope to report on these experiments in the near future.

PICK'S DISEASE WITH ATROPHY OF THE TEMPORAL LOBES

A CLINICOPATHOLOGIC STUDY

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In the majority of instances, the focal atrophy in Pick's disease is that of a combined frontotemporal or frontotemporoparietal type. Because of such widespread lesions it has been difficult to correlate the individual symptoms with any anatomic localization, and it would appear more suitable to analyze cases in which there is selective involvement of either the frontal or the temporal area. Cases in which there is exclusive, or predominant, atrophy of the temporal lobes are comparatively rare. It is the purpose of this report to analyze such a case and attempt a clinical and pathoanatomic correlation.

REPORT OF A CASE

History.—A. C., a white housewife aged 59, married, was admitted to the hospital on March 14, 1933, because of personality change and loss of memory. The family history was characterized by numerous instances of alcoholism and personality disorder and by the occurrence of a psychosis described as "religious mania" in a maternal uncle. The patient had always been considered intellectually dull and emotionally unstable. The medical history was essentially without significance, except that at the age of 46 it was found that a test of her blood gave a positive reaction for syphilis and she received a course of intravenous injections. The onset of the present illness was insidious, occurring about five years prior to admission, with increasing irritability, ideas of marital infidelity and signs of progressive impairment of memory. It was noted that she could not remember the names of objects, and she became unable to cook because she could not recall the names of common vegetables and meats. She became childlike, naive and overly religious. During the year prior to admission she failed to recognize old acquaintances and was unable to recall past events spontaneously, but could remember fairly adequately when assisted by her husband. She became unable to do simple tasks, since she often forgot what she intended to do. As she could recall only the use and not the names of ordinary household objects, it finally became necessary to convey her

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From the Neuropsychiatric Institute, the University of Michigan; R. W. Waggoner, M. D., Director.

Read at the Ninety-Fifth Annual Meeting of the American Psychiatric Association, Chicago, May 10, 1939.

wishes by acting in pantomime. She frequently complained of dizziness and was awkward in her movements. Nocturnal restlessness was marked, and during the day she wandered aimlessly through the streets. Transitory episodes of hyperactivity, excitement and confusion gradually became more frequent.

Physical Examination.—The patient was well developed, and fairly well nourished. The skin and hair showed senile changes. The heart was of normal size, but a soft blowing systolic murmur was heard over the aortic area. The blood pressure was 124 systolic and 100 diastolic and the peripheral arteries showed increased resistance. There was moderate arteriosclerosis of the retinal vessels. The left pupil was slightly larger than the right, and both were somewhat irregular; they reacted promptly in accommodation but sluggishly to light. The other cranial nerves were normal. The superficial and deep reflexes were in order, and no pathologic reflexes were elicited. Examination of the urine and blood gave essentially normal results. The Kahn reaction of the blood was negative on repeated examinations. The cerebrospinal fluid contained 7 cells per cubic millimeter; there was no increase in protein, and the colloidal gold and mastic curves were flat.

Psychiatric Examination.[1]—General Behavior: In her general reactions the patient demonstrated an increased psychomotor drive and marked logorrhea. The mood was predominantly euphoric, in reaction to states of religious ecstasy accompanied by auditory and visual hallucinations. There were sudden shifts to transitory irritability, when she expressed vague ideas of persecution, relating to the infidelity of her husband and the activities of the nurses.

In the psychologic field the most outstanding features were disturbances in the speech mechanism and intellectual processes. In test situations the patient cooperated well, but her capacity to attend varied between unusual tenacity and distractibility, depending on whether she succeeded or failed. She was often aware of her intellectual defects and became irritable when unable to respond correctly.

Speech: The patient was right handed, and prior to the onset of the present disorder had had no difficulties in articulation, expression or reception of speech. In spontaneous speech she was talkative, but her pronunciation and intonation were normal and there was no jumbling of syllables or jargon speech. However, her conversation was somewhat disconnected and hesitant, since words were frequently omitted. This was due to her inability to recall the exact word she desired, necessitating circumlocutions by substitute words or descriptive phrases in order to make her meaning clear. In general, the patient was able to understand spoken language, as shown by her ability to respond to ordinary requests in the ward, as well as to follow directions in test situations. Her reception of speech was impaired only when she was given complex or lengthy instructions or when her difficulty in recall was involved. She was able to repeat simple words or short sentences, but failed if the sentences were long or contained much unfamiliar material. In automatic word series the patient's performance was fairly good. She correctly counted from 1 to 100 and named the days of the week. In saying the alphabet she made mistakes, but she repeated it correctly after the examiner. Her greatest difficulty was in recalling the proper symbols for objects and conditions, and she consistently failed in all naming tests. She was always able to recognize an object and pointed to the correct article on oral or written command, or when a duplicate object was shown or placed in her hand. However, when required to name it

1. The psychologic investigations were carried out by the late Dr. Albert M. Barrett.

aloud she usually misidentified it, gave long circumstantial descriptions or illustrated the use of the object. For example, a matchbox was called "the box with a little of the many little things." In spite of this, her answer was usually in the correct general category and approximated the right response. For example, in color tests she usually misidentified the shade, but she never responded with words other than the names of colors. Her responses were extremely variable, and often she failed to name an object which she had correctly identified a few moments before. On the other hand, in spontaneous conversation she frequently used names of objects in an effortless manner, only to fail a few minutes later in recalling these words in a test situation. When she was unable to apply any name to an article, she responded in a stereotyped manner with, "That's funny; it's off my mind." Attempts were made to retrain the patient in naming, but after a few minutes she returned to her original level. The patient recognized her impairment in word finding and wrote out a list of names and studied this for long periods, only to fail when she attempted to recall the words.

Writing: The patient was able to write spontaneously in a legible manner, to copy paragraphs and to write from dictation without difficulty. She was able to write automatic word series with only minor errors. Her naming defect was even greater when she attempted to write her responses, and she frequently misspelled words that she named correctly. There was often disparity in her simultaneous verbal and written productions; for example, when shown matches she said "watch" and wrote "safety match." When she attempted to remember several test names or sentences long enough to write them, she failed completely.

Reading: She read printed words, paragraphs and script without difficulty, responded to written commands and understood the meaning of words. However, in reading aloud she occasionally verbalized a word incorrectly and the consequent misunderstanding was evident in her responses.

Drawing: The patient's sketches of concrete objects, although crude, were essentially correct. She was able to select and group like geometric figures and to copy them accurately and rapidly. However, when asked to draw geometric figures she became confused and was unable to proceed; for example, when asked to draw a circle she finally wrote "a circle."

Gnosia and Praxia: The patient did not show any disturbances in the recognition of familiar objects or in the execution of simple mechanical movements. The simpler movements of Head's tests were usually carried out correctly, but there were errors in the more complex mirror movements.

General Intellectual Functions: The patient was correctly oriented for place and persons and approximately for time. The results of memory tests varied considerably, depending on the complexity and type of the test material. Her remote and recent memory were surprisingly clear on historical and factual data relating to her personal life. She could repeat six digits forward and four backward on auditory stimulation and seven digits forward on visual stimulation. However, a marked memory defect became apparent when the material was complex and abstract or when there was a long interval before response. Thus, in auditory and visual memory for concrete words she approximated her Binet mental age, but fell below it in memory for abstract words. The memory impairment was especially apparent when she attempted to recall paragraphs, details of a complex picture, nonsense syllables or any material which required the ability to synthesize or to form new associations for the purpose of remembering. She was able to calculate correctly, appreciated the relative values of coins and could make change rapidly and accurately. In her general comprehension the same disparity was

noted between her inability to understand complex or abstract subjects and her good comprehension for simple practical matters. She did not comprehend what was desired in the usual tests for absurdities and abstract matters. Although she verbally described the floor plan of her home, she could not understand what was meant by a line drawing of the arrangement and could draw only vertical objects, such as chairs and tables. In the ball and field test of the Binet series she was unable to understand the problem. On the Stanford-Binet test, the patient attained a mental age of 7.5 years and an intelligence quotient of 46. Her only success above the 9 year level was in the return of digits. The vocabulary test was especially difficult for her because of her inability to find descriptive words, and she could define only two words of the entire series. In nonlanguage performances the patient achieved an average mental age of 11.1 years, the results being generally superior to the language performances.

Clinical Course.—During the patient's nine weeks' residence in the hospital her fundamental disturbances in thinking and word finding remained unchanged, but her behavior reactions varied constantly. She was euphoric, ecstatic and hallucinated and prayed loudly for hours, or was irritable and occasionally assaultive. She showed little interest in ward tasks or in events going on about her, and her attention was largely directed toward her personal affairs and concern over her memory and speech disorder. She was discharged on May 27, 1933, but continued to be a management problem at home, wandered about the streets, associating with undesirable people, and had frequent temper outbursts. She was therefore admitted to Ypsilanti State Hospital on Nov. 25, 1933. From this time, further psychologic testing became difficult because of intensification of her psychotic reactions. However, when she was accessible no appreciable change could be demonstrated in her aphasic and thinking disorder. During the ensuing years her paranoid and religious trends became more marked and the episodes of excitement more frequent and prolonged. There was gradual narrowing of her mental horizon to the point at which she spent most of her time shouting prayers in a perseverating manner. An encephalogram performed on Jan. 30, 1934 revealed only moderate and symmetric dilatation of the lateral ventricles. She died on March 9, 1938.

Autopsy.—There were bilateral lobar pneumonia, mild syphilitic aortitis, generalized arteriosclerosis, chronic cholecystitis and cholelithiasis, cyst of the left ovary and passive congestion of all organs.

Macroscopic Examination: The brain weighed 1,235 Gm. The leptomeninges were moderately thickened, and there was mild sclerosis of the basal vessels. The cerebral hemispheres were of equal size. In the temporal lobes there was symmetric circumscribed atrophy, somewhat more pronounced on the left. The atrophy involved the pole of the temporal lobe, the anterior one third of the superior temporal gyrus and the entire middle and inferior temporal and fusiform gyri. In sharp contrast, the hippocampus and the posterior two thirds of the superior temporal gyrus were well preserved (fig. 1). The atrophic convolutions were extremely narrow, "knife blade" in type, with a rough, yellowish brown surface, and the sulci were wide and gaping. The convolutions of all other lobes were not visibly atrophic. Coronal sections and large Nissl preparations demonstrated, in addition to involvement of the aforementioned areas, severe symmetric atrophy of the islands of Reil and moderate bilateral atrophy of the uncus, lingual gyrus and base of the frontal lobe. In all areas involved, the gray and white matter were shrunken and poorly demarcated. The temporal horns were dilated. The remainder of the cortex, basal ganglia, brain stem and cerebellum were grossly normal.

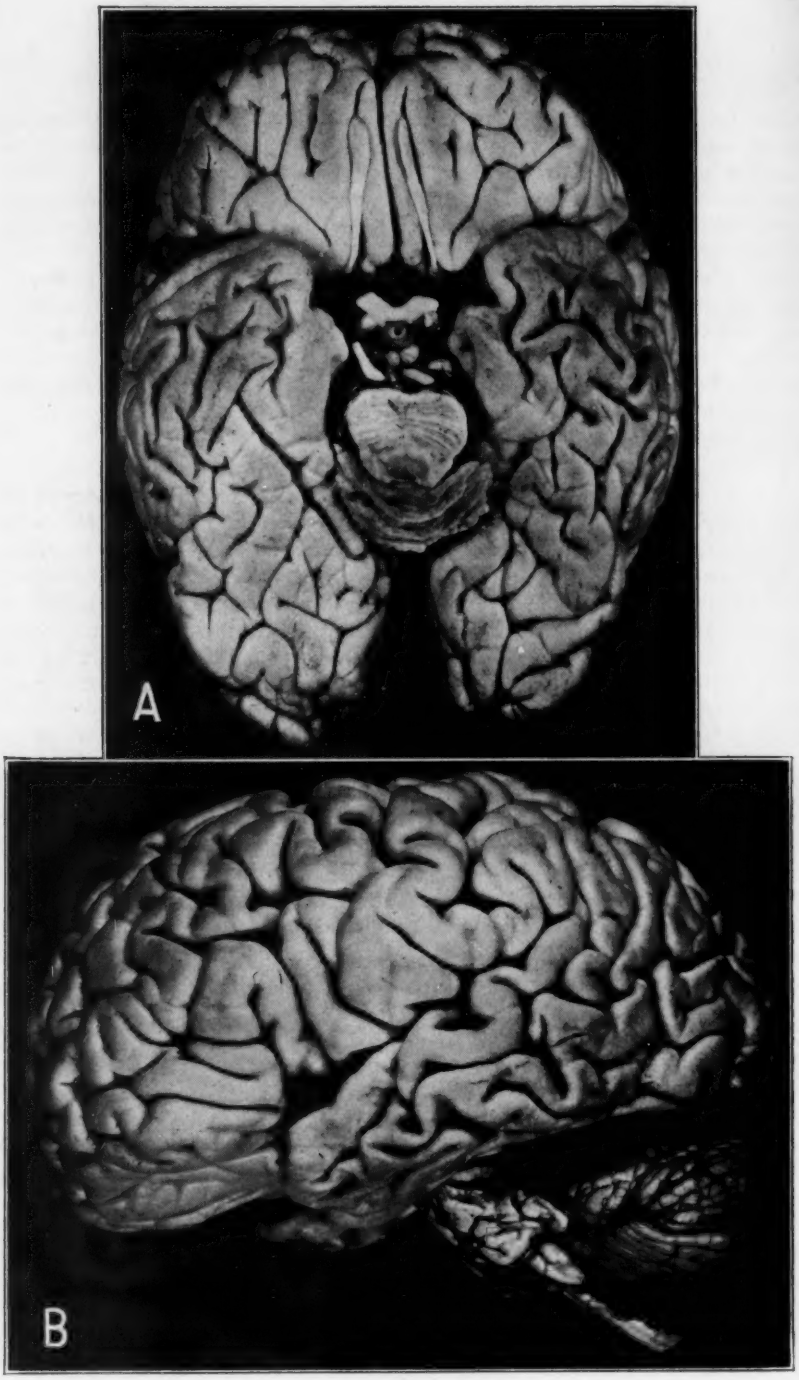

Fig. 1.—*A*, Basal surface of the brain, showing symmetric atrophy of both temporal lobes, slightly more pronounced on the left. The atrophy involves the temporal pole and inferior temporal and fusiform gyri and encroaches slightly on the uncus, but spares the hippocampus. *B*, Lateral aspect of the brain, showing atrophy of the temporal pole, anterior third of the superior temporal gyrus and entire middle and inferior temporal gyri. Note the lack of involvement of Wernicke's and Broca's zones.

Microscopic Observations: Examination of Nissl preparations under low magnification (fig. 2) disclosed that the cortex of the middle and inferior temporal and fusiform gyri was reduced by about one-third to one-half its normal width. This reduction was mainly accounted for by the far advanced degeneration and shrinkage of layers I, II and IIIa, while lamina IV remained intact and laminas IIIb, V and VI showed mild degeneration, except in the fusiform gyrus, in which the deeper layers were also severely involved. From the fusiform gyrus the degeneration extended into the hippocampal gyrus for a short distance only, entirely sparing the subiculum, the cornu ammonis and the dentate gyrus. From the middle temporal gyrus it extended into the inferior part of the superior temporal gyrus, but spared most of the cortex of the latter convolution, including the transverse gyri, or Heschl's convolutions. The degeneration of the insular region was also sharply demarcated from the surrounding frontoparietal and

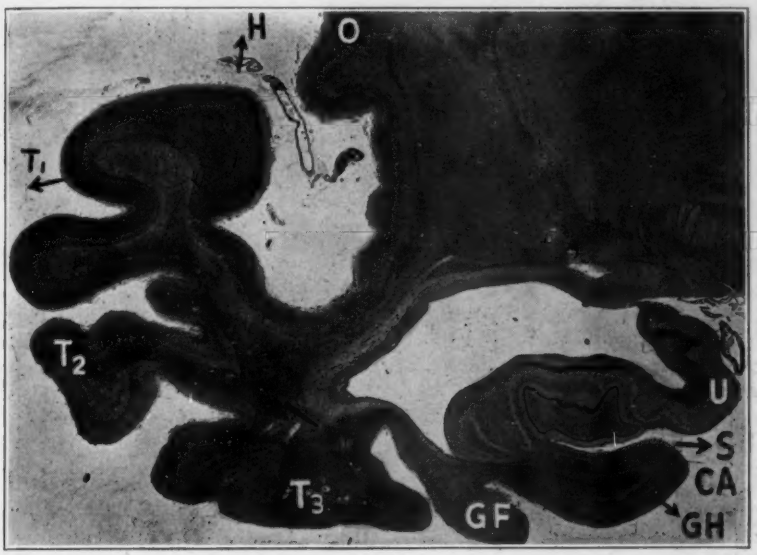

Fig. 2.—Left temporal region at the level of the mamillary bodies, showing severe atrophy and degeneration of the gray and white matter of the affected gyri. Note the normal cytoarchitecture in the superior temporal gyrus (T_1), Heschl's convolutions (*H*), the opercular region (*O*) and the cornu ammonis. Nissl stain.

In this photograph and in the accompanying photographs, *CA* indicates the cornu ammonis; *GF*, the gyrus fusiformis; *GH*, the gyrus hippocampi; T_1, T_2 and T_3, the superior, middle and inferior temporal gyri, respectively; *U*, the uncus, and *S*, the subiculum.

temporal operculums. The gyral white matter of the atrophic regions, including the capsula extrema and the capsula interna, was shrunken and stained deeply.

Comparison with the Weigert picture showed corresponding involvement of the myelin sheaths (fig. 3*A*). There were distinct demyelination of the white matter and loss of myeloarchitecture in the middle and inferior temporal and fusiform gyri and in the insula, contrasting with the preserved myelin structure in the superior temporal gyrus and in the hippocampus. The degeneration of the gray matter was

largely restricted to the tangential and supraradial fibers, and that of the white matter to the association fibers, sparing Türck's bundle.

Holzer preparations (fig. 3 *B*) showed dense, isomorphic gliosis of the white matter, restricted to the atrophic gyri, and marginal gliosis in the cortex.

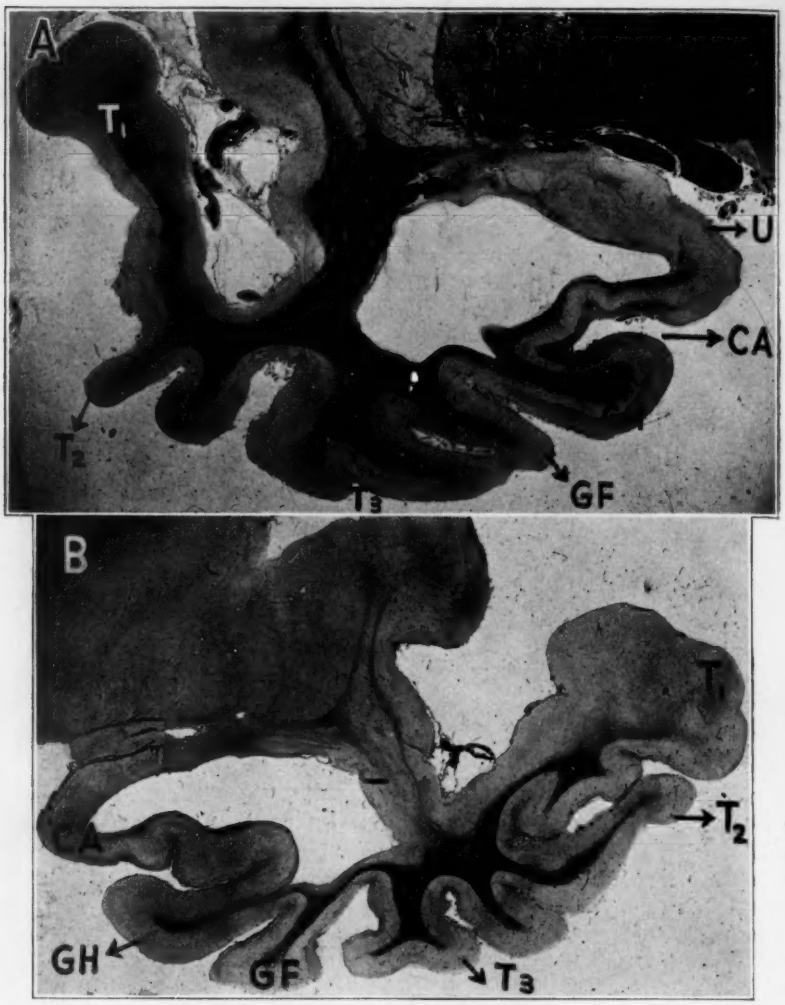

Fig. 3.—*A*, Weigert photograph corresponding to figure 2, showing demyelination in the gray and white matter of the atrophic gyri. *B*, Holzer photograph corresponding to figure 2, showing gliosis of the white matter in the involved gyri, extending slightly into the base of the superior temporal convolution and into the gyrus hippocampus.

In the pole of the temporal lobe, the involvement was equally severe in the three temporal gyri and extended into the uncus and amygdaloid nucleus. The atrophy of the temporal convolutions extended posteriorly into the area parietalis basalis and

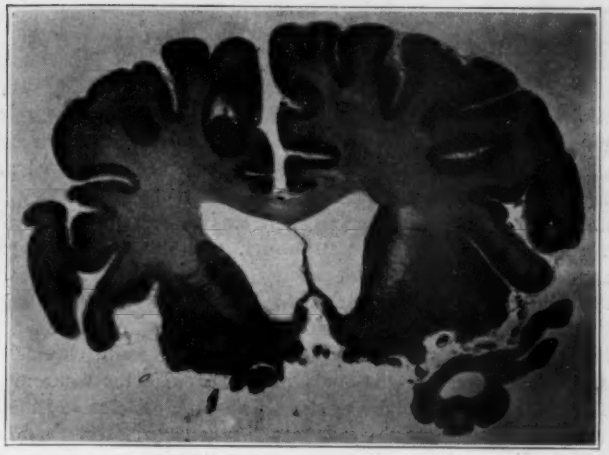

Fig. 4.—Moderate atrophy of the base of the frontal lobes, restricted to the orbital and rectus gyri; severe atrophy of the entire cross section of the right temporal pole. Nissl stain.

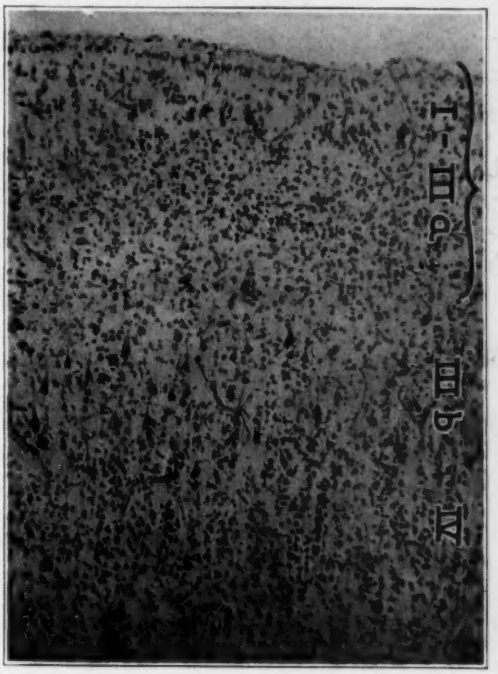

Fig. 5.—Severe atrophy, loss of neurons and dense accumulation of glia cells in laminas I, II and IIIa, milder involvement of lamina IIIb and normal lamina IV. Nissl stain; Zeiss objective, 16 mm.; ocular, no. 2.

into the lingual gyrus, but the degeneration of these regions was mild. In the frontal lobe there was moderate symmetric atrophy of the entire base, which was restricted to the rectus and orbital gyri and was sharply demarcated from the adjacent inferior frontal convolution, including Broca's area (fig. 4). The cytoarchitecture and myeloarchitecture of all other convolutions in the frontal, parietal and occipital areas were normal.

In the degenerated areas the few remaining neurons were shrunken and the glial nuclei greatly increased (fig. 5), and in the most severely involved areas there was a spongy state. Acute degenerative, progressive and inflammatory phenomena were absent. In Braunmühl preparations there was reduction of axis-cylinders and of the intracellular neurofibrils. Senile plaques, Alzheimer fiber changes, inflated elements and argentophilic inclusion bodies were absent. There were scant deposits of fat in the neurons, glia and walls of blood vessels. The last were moderately thickened, but not proliferated. The iron content was not increased. In the well preserved areas of the cortex there were nonspecific chronic changes of the neurons, diffuse increase in glia and mild reduction of the white matter. The pia-arachnoid was thickened. There was moderate atherosclerosis of the meningeal vessels, with scattered perivascular scars in the underlying cortex, least evident in the atrophic regions. In the basal ganglia, especially in the corpus striatum, there was some increase of glia, which contained greenish pigment but no other changes. The white matter of the cerebellum showed moderate rarefaction, but its gray matter, as well as the entire brain stem and cervical portion of the cord, were normal.

COMMENT

Clinical Features.—A review of the literature reveals that the outstanding clinical manifestations in cases of Pick's disease with atrophy of the temporal lobes are aphasia and a certain type of dementia.

Pick [2] first pointed out that the aphasia in these cases is of an amnesic type and attributed this to the localization of the atrophy in the middle and inferior temporal gyri, leaving Wernicke's zone intact. He noted that further disorganization of speech occurred only when other regions, such as Broca's area, also became involved. Although the early investigations by Pick, Liepmann [3] and others were limited to gross observations in cases of atrophy of both the frontal and the temporal lobes, subsequent reports essentially confirmed Pick's observations. Since the recognition of Pick's disease as a definite entity, several cases in which atrophy was restricted to the temporal lobes have been reported, in all of which amnesic aphasia was a prominent symptom (Rosenfeld,[4] Stertz [5] and Schneider [6]). Rosenfeld's patient showed uncomplicated amnesic

2. Pick, A.: Zur Symptomatologie der linksseitigen Schläfenlappenatrophie, Monatschr. f. Psychiat. u. Neurol. **16**:378, 1904.

3. Liepmann, H.: Ein Fall von Echolalie, Neurol. Centralbl. **19**:389, 1900.

4. Rosenfeld, M.: Die partielle Grosshirnatrophie, J. f. Psychol. u. Neurol. **14**: 115, 1909.

5. Stertz, G.: Ueber die Picksche Atrophie, Ztschr. f. d. ges. Neurol. u. Psychiat. **101**:729, 1926.

6. Schneider, C.: Ueber Picksche Krankheit, Monatschr. f. Psychiat. u. Neurol. **65**:230, 1927.

aphasia, which the author attributed to involvement of the "naming centres" located in the middle and inferior temporal and fusiform gyri. Stertz noted in his case, in addition to the amnesic aphasia, disturbances in comprehension of speech, impairment of reading, writing, logorrhea and echolalia, but no impairment of spontaneous speech and no evidence of paraphasia. These manifold symptoms were attributed by Stertz to loss of the higher forms of speech, with preservation of more primitive expressions, such as echolalia and logorrhea, as well as to the specific localization outlined by Pick. This systematic deterioration of the speech mechanism was regarded by Stertz as characteristic of the aphasia in Pick's disease. A more cautious attitude was adopted by Schneider, who expressed the opinion that the aphasic disturbances in Pick's disease are not specific, although he remarked that the amnesic type usually predominates. In our case the speech disturbance consisted essentially of impairment in word finding, which was equally apparent in speaking, writing and reading, with only minimal disturbance in repetition and in expressive and receptive mechanisms. It seems, therefore, that amnesic aphasia is an important feature in this form of Pick's disease and, as will be discussed later, is probably based on the same underlying mechanism as the dementia.

A certain type of mental deterioration has been noted in cases of atrophy of the temporal lobes, which cannot be attributed to the disturbances in the speech mechanism per se. This consists of reduction in associative and creative thinking, in judgment and insight, whereas memory, orientation and attention remain relatively preserved for some time. The deterioration may be defined as a loss of higher mental faculties, with relative preservation of the more elementary functions. According to Goldstein and Katz,[7] the essential disturbance in Pick's disease is loss of the abstract or categorical attitude, with preservation of the concrete attitude, which is equally apparent in all psychic functions. This Goldstein and Katz attributed to atrophy of the frontal lobes, but in the light of our observations it is suggested that similar disturbances may result from involvement of the temporal lobes. Thus, we noted signs of spatial disorientation, loss of memory for and comprehension of abstract material, as contrasted with retention of general orientation and only mild impairment of memory for concrete events. It may therefore be inferred that this type of deterioration is characteristic of Pick's disease, regardless of the localization of the atrophy.

Other symptoms commonly observed in Pick's disease, such as stereotypies, episodes of hyperactivity and changes in mood and in personality, have also been noted in cases of atrophy of the temporal lobes, while loss

7. Goldstein, K., and Katz, S. E.: Psychopathology of Pick's Disease, Arch. Neurol. & Psychiat. **38**:473 (Sept.) 1937.

of initiative, impulse and will is usually attributed to atrophy of the frontal lobes. Psychotic manifestations are as a rule absent, but in our case paranoid-hallucinatory trends were prominent.

In all 4 cases reviewed here, the onset of the disease occurred in the middle of the sixth decade of life, and the duration was from ten to twelve years. The neurologic status was essentially normal. So far as is known, there were no significant hereditary trends or other etiologic factors. In spite of a history of syphilis in our case, there were no clinical, serologic or pathoanatomic indications of syphilis of the central nervous system.

Pathoanatomic Features.—The pathoanatomic observations in cases of Pick's disease with atrophy of the temporal lobes are remarkably constant (besides the 4 cases discussed, the review is based on 7 additional cases described pathoanatomically, but not clinically, by Spatz [8]). The atrophy is bilateral, symmetric and selective, involving the pole and the midportion of the temporal lobe, namely, the middle and inferior temporal and the fusiform gyri. In contrast, the dorsolateral portion of the superior temporal gyrus, including Heschl's convolutions, and the hippocampus, including the subiculum, dentate gyrus and cornu ammonis, are usually well preserved. The atrophy occasionally extends for a limited distance into the hippocampal and lingual gyri, and is especially likely to involve the insula, as in our case. Spatz suggested that the primary focus of the atrophy may occur either in the fusiform gyrus or in the pole of the temporal lobe. Histologically, the upper layers of the cortex are more severely affected than the lower layers, and there is also involvement of the association, but not of the projection or the commissural, fibers. The condition is a simple degeneration of the parenchyma; signs of inflammation, atherosclerosis and senility, such as senile plaques and Alzheimer neurofibril changes, are absent. In none of the 4 cases were there any inflated elements or argentophilic inclusion bodies. In the rest of the brain there were only mild, diffuse microscopic changes.

It may be inferred that the anatomic criterion of this disorder is the involvement of definite convolutions and cortical laminas. Gans [9] demonstrated in cases of Pick's disease with involvement of the frontal lobes that the atrophy was restricted to those cytoarchitectural fields of Brodmann which correspond to phylogenetically and ontogenetically younger areas of the brain. Onari and Spatz [10] found the same principles to apply

8. Spatz, H.: Ueber die Bedeutung der basalen Rinde, Ztschr. f. d. ges. Neurol. u. Psychiat. **158**:208, 1937.

9. Gans, A.: Betrachtungen über Art und Ausbreitung des krankhaften Prozesses in einem Fall von Pickscher Atrophie des Stirnhirns, Ztschr. f. d. ges. Neurol. u. Psychiat. **80**:10, 1922.

10. Onari, K., and Spatz, H.: Anatomische Beiträge zur Lehre von der Pickschen umschriebenen Grosshirnrinden-Atrophie, Ztschr. f. d. ges. Neurol. u. Psychiat. **101**:470, 1926.

in cases of atrophy of the temporal lobes. The temporal gyri which are involved correspond to Brodmann's area temporalis propria (21 and 20), area temporopolaris (38) and area fusiformis (36). These are phylogenetically younger areas and develop in the sequence mentioned in primates, attaining their highest development in man. Ontogenetically, they are the last to myelinate, and it has been pointed out by Ariëns Kappers and his associates [11] that "in the phylogenetic scale of mammals, especially in man, the inferior temporal region shows a spreading out and differentiation in different directions where new fields arise which do not become medullated ontogenetically until later." The uninvolved portions of the temporal lobe are the genetically older area supratemporalis, which includes Wernicke's zone and Heschl's convolutions, and the area hippocampi. Although the atrophy tends to overlap somewhat these boundaries, Spatz, in agreement with Gans, regarded the aforementioned changes, as well as the predilection of the degeneration for the upper layers (which represent the association cortex), as evidence that Pick's disease is a system disorder. In our case the similar localization of the atrophy in the temporal lobes and of the accompanying mild atrophy in the orbital and rectus gyri of the frontal lobes in general tends to substantiate the views of Gans and Spatz. It is difficult to interpret the involvement of the insular region on the same phylogenetic basis, because of the complex cytoarchitectural structure and development of this area, although Rose [12] expressed the belief that the major part of the insula is a genetically younger region.

CONCLUSIONS

The study suggests that in Pick's disease the impairment of psychic functions occurs in a systematic manner, so that higher levels are disturbed before the more primitive levels. This would explain not only the characteristic dementia but also the predominantly amnesic aphasia in cases of atrophy of the temporal lobes. The fact that amnesic aphasia frequently occurs as an initial phase in the course of other speech disturbances implies that it represents a systematic disturbance in the highest levels of the speech mechanism. Its prominence in Pick's disease, in which there is a general "loss of the categorical attitude," is in keeping with Goldstein's [13] view that "amnesic aphasia is not a primary disturbance

11. Ariëns Kappers, C. U.; Huber, G. C., and Crosby, E. C.: The Comparative Anatomy of the Nervous System of Vertebrates, Including Man, New York, The Macmillan Company, 1936, vol. 2, p. 1673.

12. Ariëns Kappers, Huber and Crosby,[11] p. 1630.

13. Goldstein, K., in Bethe, A.; von Bergmann, G.; Embden, G., and Ellinger, A.: Handbuch der normalen und pathologischen Physiologie, Berlin, Julius Springer, 1927, vol. 10, p. 792.

of the speech process, but a disturbance of the categorical attitude, which is a necessary condition for word finding." From an anatomic standpoint, the aphasia cannot be attributed to a specific localization, even though the restriction of the lesion to certain convolutions of the temporal lobes may have a determining influence. Thus, the involvement of additional areas, such as the insula, does not essentially alter the amnesic aphasia, as seen in our case. In other cases (Stertz), additional aphasic symptoms occur in spite of the similar localization of the lesions. Neither can the dementia be related to generalized involvement of the brain, since the latter is mild in cases of Pick's disease with atrophy of the temporal lobes, in contrast to that in diffuse degenerative disorders. It seems, rather, that the involvement in Pick's disease of genetically younger areas which are concerned with higher associative functions would result in the systematic disturbance in the highest levels of the speech and thinking mechanisms.

VARIATIONS IN THE CARBON DIOXIDE CONTENT OF THE BLOOD IN EPILEPSY

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The observation that epileptic seizures can be precipitated by overventilation was reported by Rosett,[1] and also by Foerster,[2] in 1924. One of us (W. G. L.),[3] in 1928, demonstrated that petit mal seizures can be temporarily abolished by breathing air containing an increased concentration of carbon dioxide. In spite of the numerous reports dealing with the effects of overventilation, there has been a curious lack of discrimination in regard to the types of seizures most readily influenced. Our studies have shown that overventilation will not precipitate all types of seizures with equal facility. In fact, overventilation seems to be almost specific for petit mal, although occasionally psychomotor seizures are precipitated. In several hundred trials, a period of overventilation which regularly produces petit mal seizures never precipitated a grand mal seizure. On the other hand, in 2 cases in which there were both petit mal and grand mal attacks, a grand mal seizure occurred when the patient resumed breathing room air after long-continued subjection to a high carbon dioxide atmosphere, which had stopped all petit mal activity as

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From the Department of Neurology of the Harvard Medical School, and the Neurological Unit of the Boston City Hospital.

1. Rosett, J.: The Experimental Production of Rigidity of Abnormal Involuntary Movements and of Abnormal States of Consciousness in Man, Brain **47**:293 (Aug.) 1924.

2. Foerster, O.: Hyperventilationsepilepsie, Deutsche Ztschr. f. Nervenh. **83**: 347, 1924-1925.

3. Lennox, W. G.: The Effect on Epileptic Seizures of Varying the Composition of Respired Air, J. Clin. Investigation **6**:23, 1928. Lennox, W. G., and Cobb, S.: Epilepsy, Baltimore, Williams & Wilkins Company, 1928.

judged by the electroencephalogram. Thus, there has been ample evidence that a relationship exists between carbon dioxide and epileptic seizures, but the nature of that relation requires elucidation.

The present report deals with an attempt to discover whether abnormal fluctuations in the carbon dioxide content of arterial or internal jugular blood occur spontaneously in epileptic patients and whether these fluctuations are causally linked to the seizure. The possibility that they are is strengthened by our observation [4] that the cortical electrical activity of normal persons is extremely sensitive to changes in the carbon dioxide content of the internal jugular blood, and by the observations of Dusser de Barenne, McCulloch and Nims [5] on the effect of changes in p_H on the cortical activity of animals. Furthermore, a study carried out with Leslie Nims and Denis Williams has shown that after overventilation the chemical changes in the blood differ in patients with petit mal from those observed in normal subjects. This study will be reported on later.

METHOD

Samples of arterial blood were obtained from any accessible artery, usually the radial. Venous blood was obtained from the internal jugular vein as described by Myerson, Halloran and Hirsch.[6] The vein, however, was punctured somewhat higher than was described by these authors, in order to avoid noncerebral venous blood from veins which empty into the jugular vein a few centimeters below its point of exit from the skull. Blood was analyzed for the carbon dioxide and oxygen contents by the Van Slyke manometric method, using 1 cc. samples. In most instances the oxygen capacity was also determined and the oxygen saturation calculated. The present report does not deal with measurement of carbon dioxide tension. We are well aware of the importance of this factor in a consideration of acid-base equilibrium, and, with Nims, we have completed a study in which all necessary determinations have been made for accurately characterizing the acid-base equilibrium. The results of this study will appear in a paper to be published with Nims and Williams.

The electrical activity of the cortex was recorded with six channels of amplification and six ink-writing oscillographs, designed and built by Mr. A. M. Grass. Connections were made from the lobes of both ears to the frontal, central and occipital areas on each side of the patient's head. Because of the difference in the carbon dioxide value for males and females, we used data from male

4. Lennox, W. G.; Gibbs, F. A., and Gibbs, E. L.: (*a*) Effect on the Electro-Encephalogram of Drugs and Conditions Which Influence Seizures, Arch. Neurol. & Psychiat. **36**:1236 (Dec.) 1936; (*b*) The Relationship in Man of Cerebral Activity to Blood Flow and to Blood Constituents, J. Neurol. & Psychiat. **1**:211 (July) 1938.

5. Dusser de Barenne, J. G.; McCulloch, W. S., and Nims, L. F.: Functional Activity and p_H of Cerebral Cortex, J. Cell. & Comp. Physiol. **10**:277 (Oct. 20) 1937.

6. Myerson, A.; Halloran, R. D., and Hirsch, H. L.: Technic for Obtaining Blood from Internal Jugular Vein and Internal Carotid Artery, Arch. Neurol. & Psychiat. **17**:807 (June) 1927.

patients and subjects only. The latter group of 50 subjects comprised physicians and students, with a few essentially normal patients. Blood from the internal jugular vein was obtained from 21 of the control group.

RESULTS

Is the carbon dioxide content of arterial or internal jugular blood abnormal in cases of epilepsy? From measurements made during the past ten years, we are able to submit the data represented in figures 1 and 2. From these data, we observe that patients with epilepsy have an abnormal distribution of carbon dioxide values. As seen in figure 1, the single determinations of the carbon dioxide content of arterial blood

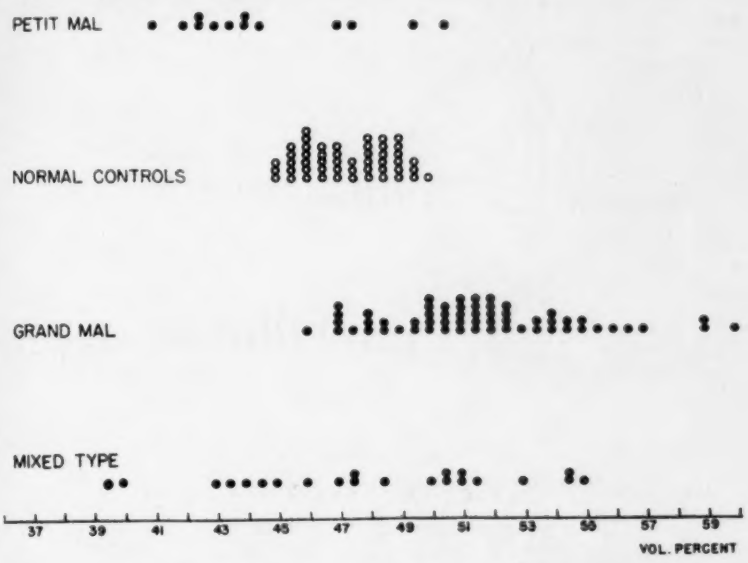

Fig. 1.—Distribution of values for the carbon dioxide content of arterial blood of 94 epileptic and 50 normal male subjects. Each dot represents a single determination of blood taken without reference to seizures. The epileptic patients are divided into three groups, as indicated. The group marked *petit mal* includes patients with petit mal and no grand mal seizures; that marked *grand mal*, those with grand mal and no petit mal seizures. The group marked *mixed type* includes patients having both petit mal and grand mal seizures. The values for the normal subjects are all found within the narrow limits of 45 to 50 volumes per cent. The values for patients with petit mal attacks tend to be on the low side of this normal zone, and those for patients with grand mal seizures, on the high side. The values for the mixed group spread out on both sides of the normal.

of 50 normal control subjects gave values between 45 and 50 volumes per cent. Of 94 patients subject to seizures, the carbon dioxide content of arterial blood was either above or below the normal zone in 70 per cent. The abnormal carbon dioxide concentration is present also in the

environment of the nerve cell, as shown by examination of blood from the internal jugular vein. As seen in figure 2, the carbon dioxide content of blood from the internal jugular vein of control persons lay between 52.5 and 56 volumes per cent. Seventy per cent of the 93 epileptic patients had values outside this normal range.

The carbon dioxide values for both arterial and internal jugular blood tend to be abnormally low in patients subject to petit mal seizures and abnormally high in patients subject to grand mal seizures. This contrast is displayed in figure 1. Of 15 patients with petit mal only, the arterial carbon dioxide content was abnormally low in 9. Of 59 patients with grand mal only, the carbon dioxide content was abnormally high in 40.

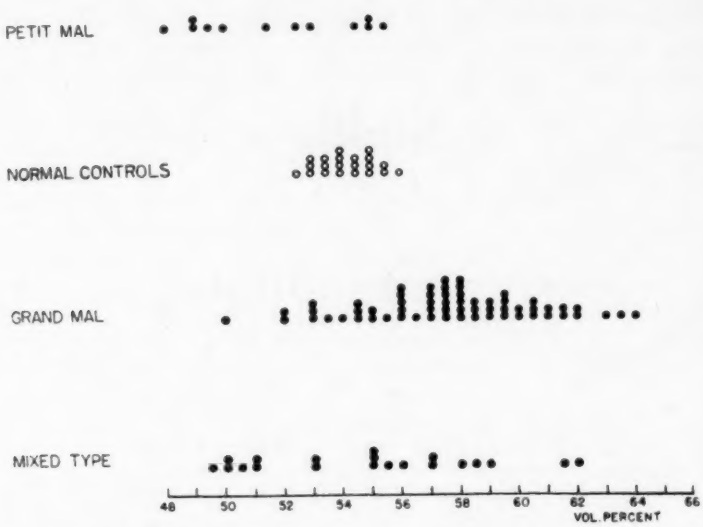

Fig. 2.—Distribution of values for the carbon dioxide content of internal jugular blood of 93 epileptic and 21 normal male subjects. Epileptic patients are divided into groups as in figure 1.

The range of normal values, from 52.5 to 56 volumes per cent, is somewhat narrower for internal jugular than for arterial blood (fig. 1). This is probably an expression of the recognized tendency of the cerebral blood vessels to correct by changes in their caliber for deviations in arterial carbon dioxide. As shown in figure 1, however, the patients with petit mal seizures have lower values than normal; those with grand mal seizures tend to have higher than normal values, and the values for those with both petit mal and grand mal attacks spread out on both sides of normal. Thus, even though there appears to be slightly less deviation from the normal range in internal jugular than in arterial blood, whatever mechanisms are operating are obviously incompetent to prevent the deviations present on the arterial side from reaching the venous side and the environment of the nerve cell.

Of 22 patients having both grand mal and petit mal, 15 had carbon dioxide values which were abnormally high or low. The distribution of values for internal jugular blood was essentially the same (fig. 2).

It is improper to conclude that because 30 per cent of the 94 epileptic patients had a normal carbon dioxide value, this proportion of patients has a normal regulation of carbon dioxide. Repeated studies on single subjects showed that the carbon dioxide content, although normal at one time, might be grossly abnormal at another. Extreme fluctuation in carbon dioxide content, rather than constant abnormality, is the most

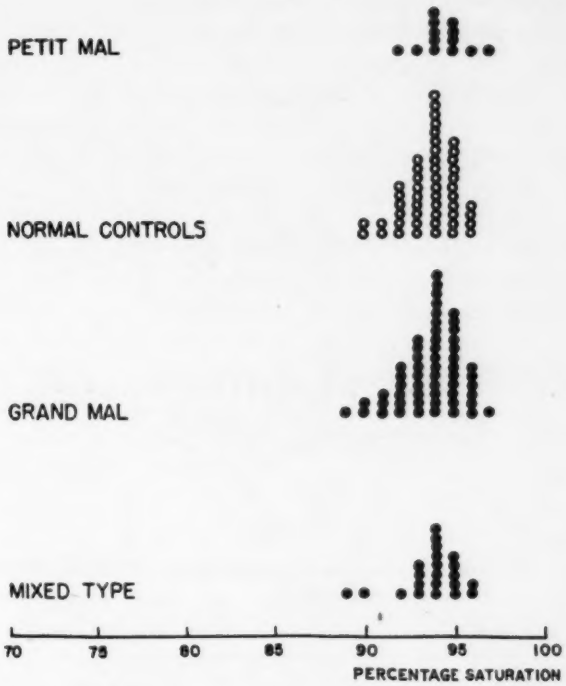

Fig. 3.—Distribution of values for the percentage of oxygen saturation of arterial blood of 90 epileptic and 50 normal male subjects. The epileptic patients are divided into groups as in figure 1.

There is no significant difference as regards the percentage saturation of arterial blood with oxygen between normal and epileptic subjects or among patients with different types of epilepsy.

striking feature of the disorder in carbon dioxide regulation in both patients with petit mal and those with grand mal.

These fluctuations are not due simply to variations in the oxygenation of the blood, as shown in figures 3 and 4, in which are given oxygen saturations of the same specimens of blood studied for the carbon dioxide content (figs. 1 and 2). There is no abnormally wide distribution

of oxygen values and no significant difference between patients with grand mal and those with petit mal seizures. The oxygen saturation of arterial blood of the control group lay between 90 and 96 per cent; only 2 epileptic patients had values above, and 2 below, this zone.

The significance of the carbon dioxide values is clear only when they are studied in conjunction with the electroencephalogram. We have shown in previous publications [7] that the different types of seizures are built on different patterns of dysrhythmia. Grand mal is associated with abnormally fast cortical activity. Petit mal is associated with waves which are alternately fast and slow, but an electrically analyzed record shows that the energy during a petit mal seizure is greatest in the slow,

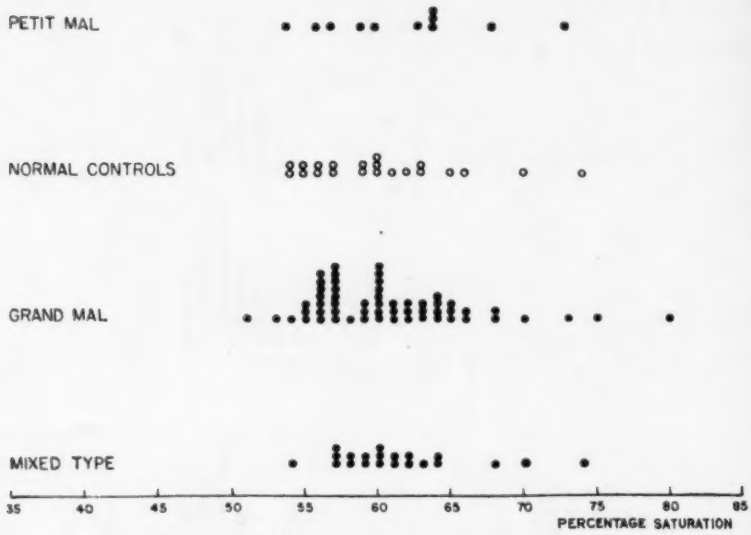

Fig. 4.—Distribution of values for the percentage of oxygen saturation of internal jugular blood of 89 epileptic and 21 normal male subjects. The epileptic patients are divided into groups as in figure 1.

The scattering in all groups is obviously greater than in figure 3. This is an expression of the fact that the cerebral blood vessels change their caliber in order to keep the carbon dioxide content more or less constant; within broad limits the oxygen content of the internal jugular blood is high or low according to the level of carbon dioxide in the arterial blood.

There appears to be no significant difference in the distribution of values for the percentage of oxygen saturation of internal jugular blood between normal and epileptic subjects nor among patients with different types of epilepsy.

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7. Gibbs, F. A.; Lennox, W. G., and Gibbs, E. L.: The Electro-Encephalogram in Diagnosis and in Localization of Epileptic Seizures, Arch. Neurol. & Psychiat. **36**:1225 (Dec.) 1936; Epilepsy: A Paroxysmal Cerebral Dysrhythmia, Brain **50**:377 (Dec.) 1937.

3 a second frequency. To these observations must be added the fact that artificially increasing the concentration of carbon dioxide in alveolar air [4a] or in arterial or internal jugular blood [4b] increases the frequency of brain waves, whereas decreasing the concentration decreases the frequency of the waves. This statement holds true both for abnormal and for normal wave patterns. These various observations are correlated. For patients with petit mal to have a lowered and patients with grand mal an increased carbon dioxide concentration is consistent with the electroencephalographic evidence.

The abnormally low carbon dioxide content of arterial and internal jugular blood in patients with petit mal is in line with our hypothesis that petit mal is to the cortex what periodic respiration is to the respiratory center. The increase in carbon dioxide content of arterial and internal jugular venous blood in patients with grand mal is in accord with our assumption that grand mal is the cortical equivalent of hyperpnea.[8]

Are spontaneous fluctuations in carbon dioxide associated with spontaneous ameliorations and exacerbations of the disorder? In 3 patients the amount of petit mal activity in a half-hour electroencephalographic record was plotted against the carbon dioxide content of arterial blood drawn while the record was being taken. The patients were studied on a number of days. A plot of the data for 1 of these patients (representative of the 3) is shown in figure 5. In all 3 cases there was an inverse relationship between the carbon dioxide content of the arterial blood and the amount of petit mal activity. That is, on the patient's good days the carbon dioxide content of his blood was high; on his bad days it was low. Knowing, as one does, that a low level of carbon dioxide tends to precipitate petit mal seizures and a high level tends to prevent them, it is reasonable to suppose that spontaneous fluctuations in the carbon dioxide level of arterial blood influence the amount of abnormal cortical activity, and hence the number of seizures which the patient is having. Thus, we believe the evidence indicates that carbon dioxide is a factor which is causally related to spontaneously occurring petit mal seizures.

More direct evidence of a causal relationship was obtained by measuring the carbon dioxide content of blood taken at short intervals (one to five minutes) from the internal jugular vein of 2 patients having frequent petit mal seizures. Data from 1 of the patients studied in this way are shown in figure 6. The carbon dioxide value for the sample of blood obtained just before the first petit mal seizure was abnormally low; during the second attack the carbon dioxide content was also low,

8. Gibbs, F. A.; Gibbs, E. L., and Lennox, W. G.: Cerebral Dysrhythmias of Epilepsy: Measures for Their Control, Arch. Neurol. & Psychiat. **39**:298 (Feb.) 1938.

and after both seizures it was high. That is, the time relations between the fluctuations in carbon dioxide concentrations and the seizure discharge were such as would prevail if carbon dioxide were a causative factor. After the first seizure the carbon dioxide fell to a lower level than at the outset, but not to as low a level as that reached just before or during the seizure. While the carbon dioxide content was at this intermediate low level, four larval seizures occurred. The oxygen content of blood drawn immediately before the seizure did not change, whereas during the seizure it increased and after the seizure it decreased. As we have shown previously,[9] these changes in oxygen content are a reflection of the increase in blood flow that accompanies a seizure. In other words, changes in oxygen content of the blood are a result, and

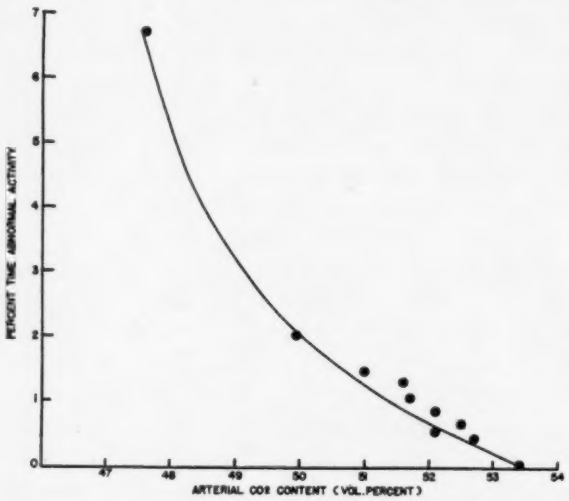

Fig. 5.—Relation between the spontaneously appearing wave and spike pattern of petit mal and the carbon dioxide content of arterial blood (patient C. G). Samples of arterial blood were obtained during ten minute runs of the electroencephalograph on successive days. The carbon dioxide content, expressed in volumes per cent (abscissas), is plotted against the percentage of ten minute periods during which the wave and spike formation was present (ordinates).

not a cause, of seizures. Consequently, the fall in carbon dioxide immediately before the seizure cannot be ascribed to changes in cerebral blood flow or in tissue oxidation. In the same patient, on another occasion, we found that arterial blood drawn during a prolonged petit

9. Gibbs, F. A.: Cerebral Blood Flow Preceding and Accompanying Experimental Convulsions, Arch. Neurol. & Psychiat. **30**:1003 (Nov.) 1933. Gibbs, F. A.; Lennox, W. G., and Gibbs, E. L.: Cerebral Blood Flow Preceding and Accompanying Epileptic Seizures in Man, ibid. **32**:257 (Aug.) 1934.

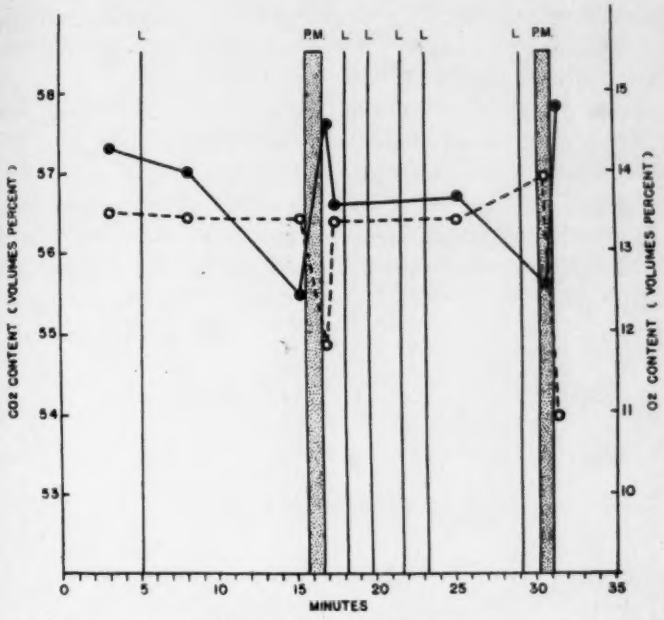

Fig. 6.—Fluctuations in the carbon dioxide and oxygen contents of internal jugular blood associated with petit mal seizures in patient C. W.

The solid dots represent carbon dioxide values; the open circles, oxygen values, both expressed in volumes per cent. *L*, at the top of a vertical line, indicates the occurrence of a larval or subthreshold seizure, one which is recorded on the electroencephalogram as a one or two second burst of wave and spike activity but which does not give clinical evidence of its presence. *P.M.*, above a stippled column, indicates a clinically obvious petit mal seizure.

Just before the first petit mal seizure a sample of internal jugular blood was obtained, which showed that the carbon dioxide had dropped from about 57 to 55.5 volumes per cent. (The rather high general level of the carbon dioxide is consistent with the fact that this patient had both petit mal and grand mal epilepsy.) With the drop in carbon dioxide, however, there was no change in oxygen, indicating that the decrease in carbon dioxide could not have been produced by a change in caliber of the cerebral vessels. After the seizure cerebral vasodilation occurred, indicated here by an increase in carbon dioxide and a decrease in oxygen. The increase in carbon dioxide was transitory; however, it dropped abruptly to a lower level than that in the first two samples of blood, and a shower of larval seizures occurred. No sample was obtained before the next seizure, but during the seizure there was vasodilation (carbon dioxide decreased; oxygen increased), which, as previously reported, is a usual occurrence, and after the seizure, vasoconstriction, as in the preceding petit mal attack.

This case indicates that when a sample of blood from the internal jugular vein is obtained just before or in the early part of a petit mal seizure the carbon dioxide level in that sample is lower than the general level being maintained in the internal jugular blood, that this drop in carbon dioxide is not necessarily the result of cerebral vasodilatation and that the cerebral vasodilatation during a petit mal seizure is not simply an attempted compensation for a high carbon dioxide level, for, on the contrary, during and preceding the seizure the carbon dioxide is low.

mal seizure contained 45.79 volumes per cent of carbon dioxide, as against 47.92 volumes per cent for blood taken before and after the seizure.

In an effort to detect the changes in carbon dioxide associated with a grand mal attack, observations were made on a patient with frequent grand mal seizures. In this case, blood was taken daily from an artery (fig. 7). It was found that the carbon dioxide content of the arterial blood climbed steadily for several days before the convulsion, and fell precipitously afterward. Since the sample drawn prior to the convulsion preceded the seizure by several hours, we cannot say

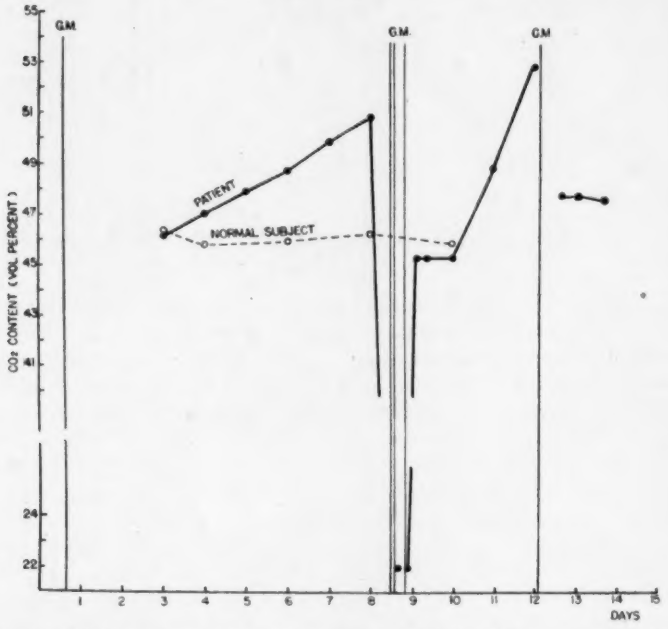

Fig. 7.—Relation of grand mal seizures to variations in carbon dioxide content of arterial blood in patient J., who was subject to frequent petit mal seizures and to grand mal attacks several times a week.

The carbon dioxide content of arterial blood was determined daily and is indicated by heavy lines and solid dots. For purposes of comparison, the carbon dioxide content of the arterial blood of a normal subject is shown by a broken line and open circles. Vertical lines, with *G.M.* above, indicate grand mal seizures.

As can be seen, there was a steady climb in the carbon dioxide content of the arterial blood before the seizures. A drop occurred with or before the seizures, whether before or with cannot be determined from these data.

whether the drop in carbon dioxide occurred just before or during the seizure. In another case of combined grand mal and petit mal seizures, we obtained samples of blood from the internal jugular vein immediately before, during and after a grand mal seizure. In this case, the carbon

dioxide was abnormally low immediately before the seizure; the sample, however, was the first obtained, so one cannot say whether the carbon dioxide had dropped from a previous high level. As the seizure started the carbon dioxide rose, fell to a new low level during the seizure and climbed gradually during the postseizure stupor. It should be noted in both the cases referred to that, although the attack clinically was of the grand mal type, the electrical record and the muscular movements during the convulsion showed a strong 3 per second (petit mal) component. This electroencephalographic pattern, i. e., a high voltage discharge of fast waves mixed with a strong 3 per second component, seems to be usual in the grand mal seizures of patients who have both grand mal and petit mal convulsions (patients with mixed types of seizures indicated in figures 1 to 4). Possibly the grand mal seizure of such a patient differs from pure grand mal type in respect to the point at which it occurs in the carbon dioxide fluctuation; i. e., it may

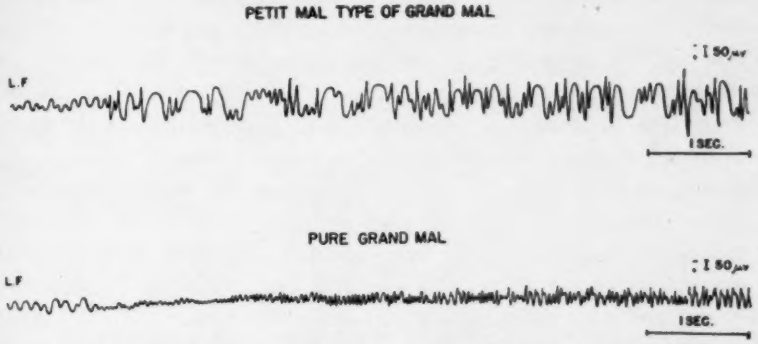

Fig. 8.—Two types of grand mal seizures recorded by the electroencephalograph. At the top is the type usually found in patients who have petit mal as well as grand mal seizures. It has a strong 3 per second component with high voltage spikes. Below is the type usually found in patients with tonic-clonic and no petit mal seizures. It has a low voltage onset with fast waves, which increase in voltage as they become slower. The signal made by 50 millivolts and the time marked by one second are shown at the right.

be that it occurs after a sudden fall in carbon dioxide. The pure grand mal seizure (fig. 8) is characterized by a crescendo burst of fast waves, which in the tonic phase are mixed with progressively slower components. These slow components are rarely as slow as 3 per second until late in the seizure. They then appear only as a transitory phase in the continuous shift to still slower frequencies. It is possible that this pure type of grand mal occurs when the carbon dioxide of arterial blood is at its height and that the drop in carbon dioxide follows the onset of the seizure. The form of the electrical record suggests that this is the case, but we have no direct evidence on the carbon dioxide

content immediately preceding a pure grand mal seizure. That abnormalities in regulation of carbon dioxide are present in pure grand mal seizures is clearly indicated, however, in figures 1 and 2.

In order to determine exactly where in the carbon dioxide fluctuation the grand mal seizure occurs, one must either piece together observations made in a number of seizures or else measure the carbon dioxide content with a continuously recording instrument. The piecing together is made hazardous by the fact that there are different types of grand mal seizures. A further difficulty is the fact that changes in the tension of carbon dioxide in brain cells may lag behind the tension of carbon dioxide in arterial or internal jugular blood. Also, determinations on a 5 cc. sample of blood drawn during a period of fifteen to thirty seconds may be too coarse, and in significant fluctuations may be averaged out. Admittedly, our data on fluctuations in the carbon dioxide content of blood before, during and after grand mal convulsions are incomplete. We present what data we have now because of their important implication and because the elaboration of adequate technic and the gathering of sufficient measurements may require considerable time.

Potassium and sodium are believed to play an important part in epileptiform discharges in the central nervous system.[10] We therefore measured the concentrations of potassium (fig. 9) and sodium in the blood of epileptic and of normal subjects (fig. 10). The distribution of values for these substances was essentially the same in epileptic and in normal subjects; there was no difference between patients with petit mal and those with grand mal seizures. Other variables which, like carbon dioxide, are more immediately involved in acid-base equilibrium show abnormalities. The nature and extent of these abnormalities will be studied in more detail before the data are presented.

COMMENT

From the data just presented, it appears that variations in carbon dioxide content of the blood of epileptic patients play a causal role in the precipitation of their seizures. But other factors must also be involved, for seizures are not precipitated in normal subjects by similar deviations in carbon dioxide content, and even in epileptic patients more extreme displacements of carbon dioxide when artificially produced are required to induce a seizure.

The questions which obtrude themselves most urgently as a result of this study are: 1. Is the shift in carbon dioxide which occurs in

10. McQuarrie, I.; Manchester, R. C., and Husted, C.: Study of the Water and Mineral Balances in Epileptic Children: Effects of Diuresis, Catharsis, Phenobarbital Therapy and Water Storage, Am. J. Dis. Child. **43**:1519 (June) 1932.

epilepsy primary, or is it an attempted compensation for a shift in some other constitutent of the blood?

2. What differences in the characteristics of acid-base equilibrium are there between epileptic and normal persons?

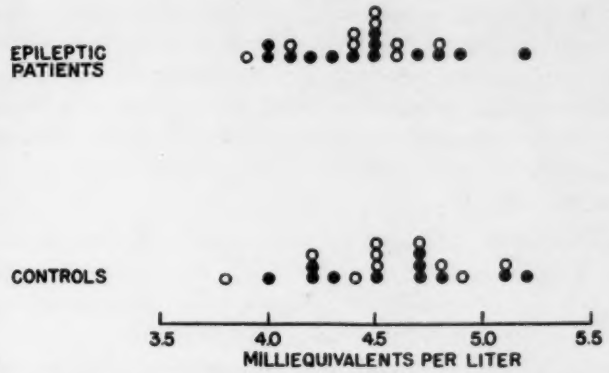

Fig. 9.—Distribution of values for potassium in internal jugular and arterial blood of 22 epileptic patients and 21 normal subjects.

No significant difference between epileptic and normal subjects can be made out.

Each dot indicates a single determination on an individual subject. The solid dots are for arterial, and the circles for internal jugular, blood.

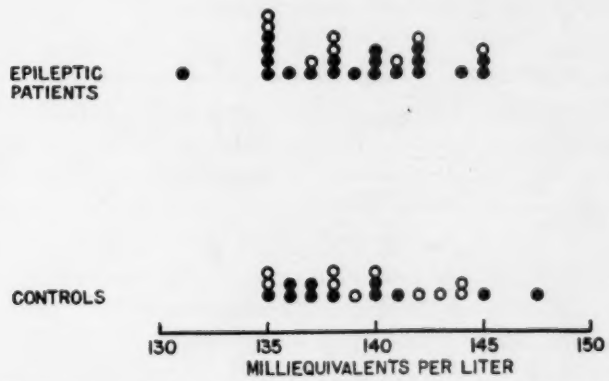

Fig. 10. Distribution of values for sodium in internal jugular and arterial blood of 28 epileptic patients and 21 normal male subjects.

No significant differences between epileptic and normal subjects can be made out.

3. Are there differences of acid-base equilibrium in different types of epilepsy?

Only when these questions are answered will it be profitable to attempt an explanation of the relation between carbon dioxide and

seizures. At present, it is enough to show the significance of these findings and to fit them into the existing framework of knowledge.

For the first time, biochemistry has provided an indicator which warns of the approach of a seizure. For the first time, a chemical abnormality can be linked with the essential mechanism of spontaneous seizures. The artificial induction of other chemical changes (anoxemia, hypoglycemia, hydration) will precipitate seizures, but on the basis of present evidence they do not appear to be the usual precipitators of the patient's spontaneous seizures, for defects of oxygen or of dextrose, of water balance or of cerebral circulation, have not been demonstrated between seizures or as a forerunner of a seizure in the usual epileptic patient.

The relationship of oxygen to seizures needs to be considered with particular care because oxygen has often been accused of playing a principal role in production of seizures and because carbon dioxide and the oxygen content of the blood occupy a reciprocal relationship. As a combustion product of oxidation, carbon dioxide is regarded as a waste product, to be rushed out of the brain in order that more oxygen may enter. However, carbon dioxide is not an inert gas, or one with a single function. Neither, as Henderson [11] has long insisted, is it a poison, but a most useful substance in the maintenance of a normal-functioning brain. According to Krogh,[12] carbon dioxide is twenty to thirty times as rapid as oxygen in crossing cell barriers. It is the quick adjuster for the maintenance of a normal and constant acid-base balance of the body.

Moreover, within physiologic limits, carbon dioxide has a more pronounced effect than oxygen on the normal and abnormal activity of the central nervous system. We have shown this to be true for the electrical activity of the cortex.[4b] Respiratory movements, tetany, hiccups and neuromuscular reflexes are more readily influenced by changes in the carbon dioxide than the oxygen content of the blood.

As for epileptic phenomena, in a series of observations we have found that pronounced changes in oxygen tension influenced the incidence of seizures,[13] but that gross abnormalities of oxygen tension or

11. Henderson, Y.: Adventures in Respiration: Modes of Asphyxiation and Methods of Resuscitation, Baltimore, Williams & Wilkins Company, 1938.

12. Krogh, A., cited by Van Slyke, D. D.: Factors Affecting the Distribution of Electrolytes, Water and Gases in the Animal Body, Philadelphia, J. B. Lippincott Company, 1926.

13. Lennox, W. G., and Behnke, A. R., Jr.: Effect of Increased Oxygen Pressure on the Seizures of Epilepsy, Arch. Neurol. & Psychiat. **35**:782 (April) 1936. Lennox, Gibbs and Gibbs.[4a]

consumption could not be demonstrated in the period between or as a preliminary to seizures.[14] We emphasize that deviation from normal carbon dioxide values occurred without coincident shift in oxygen values. This proves that abnormal concentrations of carbon dioxide are not simply a reflection of abnormal concentrations of oxygen. Furthermore, the arteriovenous difference in oxygen concentration was not abnormal in epileptic as compared with nonepileptic subjects (fig. 11), which shows that the deviations in carbon dioxide content of the internal jugular blood were not due to abnormalities in cerebral blood flow. Furthermore, there was no arteriovenous difference in oxygen concen-

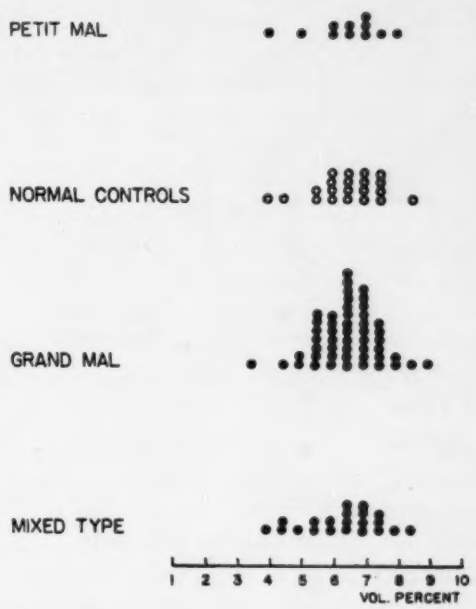

Fig. 11.—Distribution of the difference in volumes per cent of oxygen in arterial and in internal jugular blood in the same cases as those shown in figure 4. Epileptic patients are divided into groups as in figure 1.

Arteriovenous difference in oxygen content is an indicator of oxygen consumption of the brain and cerebral blood flow. No significant difference appears between epileptic and normal subjects or among patients with different types of epilepsy.

tration between patients with petit mal and those with grand mal seizures.

14. Lennox, W. G., and Gibbs, E. L.: Oxygen Saturation of the Arterial Blood in Epilepsy, Arch. Neurol. & Psychiat. **35**:1198 (June) 1936; Oxygen Saturation of Blood Draining the Brain and the Limbs of Patients with Epilepsy, ibid. **36**:13 (July) 1936.

The carbon dioxide concentration of arterial blood does, of course, influence cerebral circulation, but we have pointed out elsewhere [4b] that the changes in circulation which occur seem to be for the purpose of protecting the brain against wide swings in the carbon dioxide tension of blood coming to the brain. In our epileptic subjects, the arteriovenous difference in carbon dioxide, as well as in oxygen, content was not abnormal. The calculated cerebral respiratory quotients for both epileptic and normal subjects approached unity. This indicates that the abnormal carbon dioxide values for internal jugular blood only mirrored the abnormal carbon dioxide values in the arterial blood, which goes to all parts of the body. Presumably, blood from veins elsewhere in the body would show corresponding deviations in carbon dioxide values. In other words, the disorder seems to involve the whole body, and not just the environment of nerve cells. The deviation in arterial carbon dioxide might be due to a disturbance of respiration, in which case the finding of spontaneous increases in breathing in relation to petit mal electrical activity [15] would be apropos. However, in some of Cobb's cases, and in all those previously reported by one of us,[16] there was no constant or significant alteration of respiration before the seizure. This was true of the patient measurements of whose blood are shown in figure 6. What seems most likely, particularly in view of the results of our studies with Nims, is that the disorder involves the mechanism regulating acid-base equilibrium, of which the respiratory center is only a part.

It is only fair to point out that speculation on this point dates from Brown-Séquard,[17] who advanced the opinion that epileptic seizures are due to an accumulation of carbonic acid in the blood. For the first time, however, laboratory evidence is presented that carbon dioxide plays a part in the occurrence of spontaneous seizures in epilepsy.

SUMMARY AND CONCLUSIONS

We have measured the carbon dioxide, oxygen, sodium and potassium contents of the arterial and the internal jugular venous blood of patients with epilepsy both in the interval between seizures and in time relation to both clinical and subclinical seizures. We find that

15. Cobb, S.; Sargant, W. W., and Schwab, R. S.: Simultaneous Respiration and Electroencephalographic Recording in Petit Mal, Tr. Am. Neurol. A. **65**:137-141, 1939.

16. Lennox, W. G.: The Physiological Pathogenesis of Epilepsy, Brain **59**: 113 (March) 1936.

17. Brown-Séquard, cited by Echeverria, M. G.: Epilepsy, New York, William Wood & Company, 1870.

whereas the concentrations of oxygen, sodium and potassium are normal in epileptic persons, the values for carbon dioxide in both arterial and internal jugular blood are abnormal in the following respects:

1. The carbon dioxide content of arterial and internal jugular blood drawn without relation to seizures was abnormal in 70 per cent of 94 patients examined.

2. In patients subject to petit mal seizures, carbon dioxide values tend to be abnormally low, whereas in those subject to grand mal seizures they tend to be abnormally high.

3. Spontaneously occurring grand mal and petit mal seizures are preceded by abnormal fluctuations in the carbon dioxide content of arterial and internal jugular blood, the time relations being such as to indicate a causal linkage between the carbon dioxide content of the blood and the seizures.

These observations are consistent with electroencephalographic evidence that the type of cerebral dysrhythmia present in grand mal seizures is in contrast to that in petit mal attacks, and that carbon dioxide has a pronounced influence on cortical rhythms. All the available evidence indicates that carbon dioxide plays a significant etiologic role in epilepsy.

EPILEPTOGENIC LESIONS OF THE BRAIN

A HISTOLOGIC STUDY

WILDER PENFIELD, M.D.
AND
STORER HUMPHREYS, M.D.
MONTREAL, CANADA

This contribution is an analysis of the histologic features of various types of focal non-neoplastic lesions of the brain. The 95 specimens studied were excised at operation in an attempt to cure patients of habitual epileptic seizures. In each case the evidence indicated that the tissue excised was the starting point for the neuronal discharge which produced focal seizures in the patient in question. These lesions have resulted from traumatic injury, healed abscess of the brain, arterial occlusion and focal ischemia. The features which are common to all these different lesions must be important in the etiology of epilepsy.

PREVIOUS WORK

The meningocerebral cicatrix which produces chronic epilepsy was studied in a series of post-traumatic cases by Foerster and Penfield.[1] They concluded that laceration of the brain results in downward growth of connective tissue from the dura with a rich plexus of vessels which intermingles with astrocytes, the fibers of which tend to be oriented upward to the surface. It was pointed out that still deeper the vaso-astral framework is the only structure capable of withstanding tension (fig. 1). The existence of actual traction from such a scar and the displacement of the cerebral structures, including even the ventricles themselves, toward the scar were emphasized.

From the Department of Neurology and Neurosurgery, McGill University, and the Montreal Neurological Institute.

Read at the Sixty-Fifth Annual Meeting of the American Neurological Association, Atlantic City, N. J., June 7, 1939.

Such words as "histologic" and "pathologic" are used in order to conform to the terminology which is compulsory for publication in the ARCHIVES OF NEUROLOGY AND PSYCHIATRY. The authors would prefer the words "histological" and "pathological."

1. Foerster, O., and Penfield, W.: (*a*) Der Narbenzug am und im Gehirn bei traumatischer Epilepsie in seiner Bedeutung für das Zustandekommen der Anfälle und für die therapeutische Bekämpfung derselben, Ztschr. f. d. ges. Neurol. u. Psychiat. **125**:475, 1930; (*b*) The Structural Basis of Traumatic Epilepsy and Results of Radical Operation, Brain **53**:99, 1930.

It was observed that in the center of such scars ganglion cells were absent and nerve fibers rare, and, furthermore, that there was evidence of progressive tissue destruction, even ten to thirteen years after injury, as shown by the occasional alteration of microglia and the presence of compound granular corpuscles about individual vessels. It was sug-

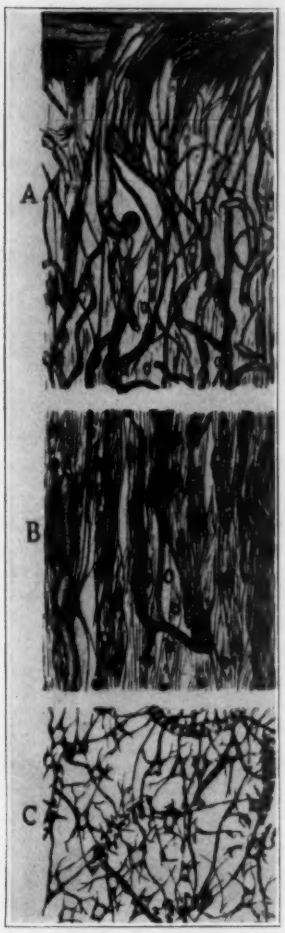

Fig. 1.—Schematic representation of the central portion of meningocerebral cicatrix. Above, collagen fibers and entering vessels. Middle panel, piloid glia (isomorphic), with numerous fine fibrils. In this zone there are few, if any, neural elements. Below, increase of astrocytes to form gliosis in the zone where ganglion cells exist (from Foerster and Penfield [1a]).

gested that such vessels might be closed from time to time by the progressive cicatricial contraction, resulting in local necrosis. These vessels, it was pointed out, anastomosed with the blood vessels of the surround-

ing brain, and this anastomosis was suggested as a possible element in the production of seizures.

Before describing the histologic changes, it may save time to review further certain pathologic principles which are explained in detail elsewhere.[2] Gliosis, or increase of fibrous astrocytes, such as is seen in the lowest panel of figure 1, occurs under abnormal circumstances, but only when nerve fibers and ganglion cells are still present. When neurons disappear in the central nervous system, the star-shaped neuroglia cells are metamorphosed into, or replaced by, piloid astrocytes. The Greek word "pilos" means "hair wrought into felt," and describes accurately the long, slender fibrils of these cells, which often arrange themselves in parallel sheaves, as shown in the middle bracket of figure 1. This sort of gliosis has been called by Jakob isomorphic. Into this network connective tissue, with its collagen fibrils, may penetrate, as shown in the upper panel, but neuroglial attachments to vessels seem largely to disappear.

ILLUSTRATIVE CASES

Of the numerous epileptogenic foci studied, a few examples will be cited to illustrate the general features of the various types of lesions.

CASE 1.—*Meningocerebral cicatrix, post-traumatic.*

History.—K. M., a man aged 26, had complained of epileptic seizures for ten years before admission to the hospital. Before the onset of his trouble he had been struck on the forehead by a piece of machinery, receiving a bilateral depressed fracture in the frontal region. He was unconscious for ten days, recovering without paralysis but with impairment of memory. Eight months after injury he began to have convulsive seizures, which increased in severity and frequency.

Operation.—Bilateral frontal craniotomy was carried out with local anesthesia. The fracture in the skull was found to be still open, the lower fragment being depressed and not covered by dura. This denuded bone was pebbled in the portion that was applied to the brain. The underlying scar was large, gelatinoid in appearance and attached to the under surface of the dura wherever this was present. There had evidently been tension, as the scar retracted when it was cut free from the dura. Numerous small, watery cystic spaces were to be seen in the scar. Bilateral excision of the meningocerebral cicatrix was carried out.

Histologic Appearance.—A cross section of a block of this tissue showed on one side the gray matter of a cortical gyrus and adjacent to it the glial scar. Patches of ganglion cells persisted in the intermediary zone. Beyond this the gelatinoid tissue contained a mixture of piloid glia and connective tissue with clusters of blood vessels passing through. In this portion few nerve fibers, but many piloid astrocyte fibrils, were present. In some zones the piloid fibrils formed sheaves (fig. 2, lowest panel), in which few nuclei occurred. Occasional fat-filled compound granular phagocytes indicated that some progressive destruction was occurring here. In more superficial areas considerable collagen was to be seen, as illustrated in the

2. Penfield, W.: Neuroglia, Normal and Pathological, in Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932, chap. 9.

middle panel of figure 2, and this increased at the surface until it became part of the overlying dense dural adhesion. This scar was tenacious and, though gelatinoid in appearance, had tensile strength and apparently contracted and pulled on the adjacent brain.

In that portion of the gray matter nearest the scar and in the islands of gray matter the astrocytes were large and fibrous (upper panel of figure 3), producing

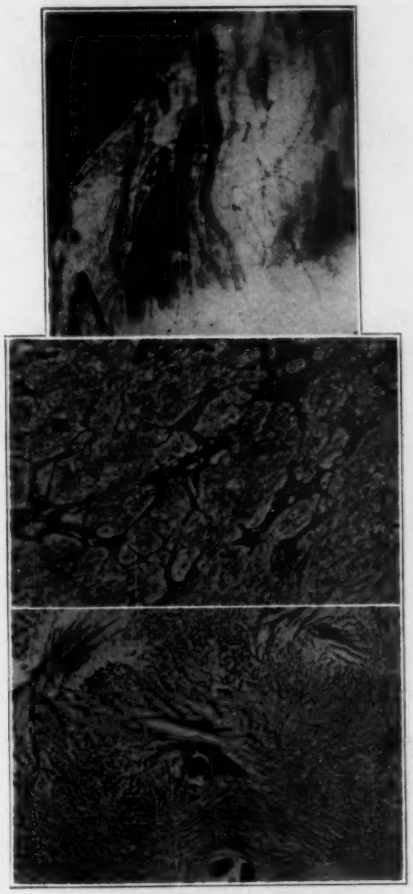

Fig. 2 (case 1).—Central portion of meningocerebral cicatrix. Upper panel, numerous vessels entering the scar from the surface; middle panel, intermixture of connective tissue and neuroglia, with much collagen; below, piloid gliosis with condensed faggots of neuroglial fibrils.

typical chronic reactive gliosis. There occurred in this zone, however, patches in which the astrocytes had undergone a very different type of alteration, clasmatodendrosis (middle panel of figure 3). This change is an acute cellular degeneration, such as may result from severe interference with local blood supply. It occurs in the vicinity of a blocked artery, which causes death of neuroglia as well as nerve

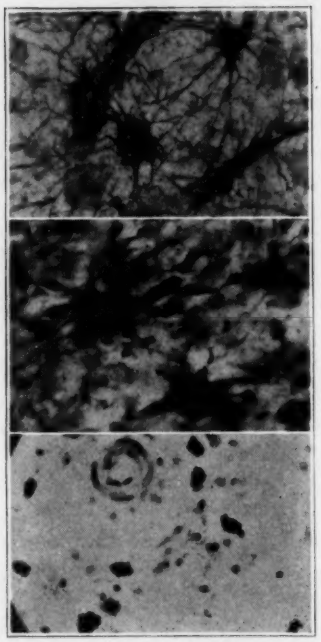

Fig. 3 (case 1).—Intermediate zone of meningocerebral cicatrix. Upper panel, gliosis in the gray matter of the intermediate zone; middle panel, clasmatodendrosis of astrocytes, the result of focal ischemia; below, compound granular corpuscles in a perivascular area of destruction.

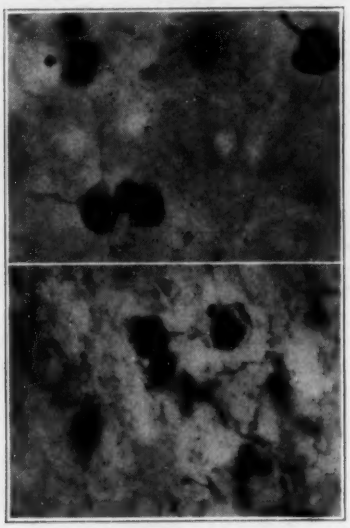

Fig. 4 (case 1).—Oligodendroglia in the gray matter of the intermediate zone. Upper panel, normal cells; lower panel, acute swelling of oligodendrocytes in a small focus.

cells. The presence of compound granular phagocytes in the same zone is shown in the lowest panel of figure 3. These fat-filled phagocytes doubtless appeared as a result of myelin degeneration, associated with death of ganglion cells.

In addition to the acute destruction of astrocytes in this frontier zone of gray matter, there was chronic degeneration of astrocytes; Nissl's plump cells appeared, as well as giant astrocytes, which were obviously dying slowly. This type of alteration is usually to be considered evidence of slowly advancing inadequacy of circulation. Acute degenerative change occurred also in the oligodendroglia. The upper panel of figure 4 shows normal oligodendrocytes in the somewhat thinned gray mantle, while the lower panel shows the swelling of oligodendrocytes, which occurred in scattered patches on the inner border of the gray mantle. At the center of most of these patches was to be seen a small blood vessel of normal appearance; consequently, we have made a study of the blood vessels themselves.

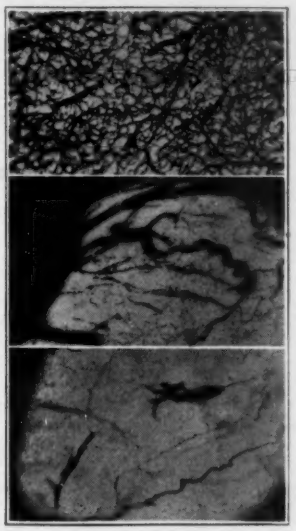

Fig. 5 (case 1).—Benzidine stain showing vascular tree. Above, normal gray matter of the frontier zone; middle panel, the intermediate zone, and below, the aganglionic central scar.

In the upper panel of figure 5 the benzidine stain demonstrates the vascular tree in the gray matter at a little distance from the frontier zone. Here were present the larger trunks of supply and a complicated system of small vascular twigs, which were at least as numerous as normal. In the frontier zone between gray matter and scar the blood vessels showed marked alteration. The main trunks gave rise to much fewer small branches than normal (middle panel of figure 5). In the center of the scar, however, a startling difference was apparent (lowest panel). The small vascular branches were obviously almost wholly absent, although the main trunks were present and often much increased. In some zones of the scar large numbers of main vascular trunks entered from the overlying meninges, as shown in figure 2. It is obvious, therefore, that the scars were well

supplied with large arteries, which, for the most part, carried blood through them, not to them.

In the small islands of gray matter which appeared in the frontier zone small vascular branches were numerous, while immediately around the islands branches disappeared almost completely. In the larger islands normal-appearing nerve cells, surrounded by normal protoplasmic astrocytes, could be seen near the center. Nearer the periphery of the island the ganglion cells were pyknotic; the astrocytes were fibrous, and chronic degenerative forms, such as Nissl's plump astrocytes and giant astrocytes, appeared. Outside the island only piloid astrocytes were to be seen, indicating the absence of nerve tissue.

The sclerotic nerve cells and the fibrous and chronic degenerative alteration of neuroglia might be considered the end result of the injury to the brain which had occurred eleven years before. However, the acute destruction of astrocytes seen in figure 3 can have been present only a few days or, at the most, a few weeks, and the fat-filled phagocytes suggest destruction of a much later date than eleven years before.

What was the nature of the destructive agency at work? If it were progressive vascular disease one would expect to find abnormality of the vessel walls and evidence of thrombosis. These were absent. If the progressive destruction were due to a toxin present in the frontier zone between brain and scar it seems unlikely that normal ganglion cells with protoplasmic astrocytes and oligodendroglia could be present at the center of the islands. On the other hand, if there was recurring arterial spasm one would expect focal destruction about normal vessels, and this was actually the case.

CASE 2.—*Meningocerebral cicatrix, postinflammatory.*

History.—M. M., a woman aged 24, complained of recurring epileptic seizures, of eight years' duration. At the age of 14 years, Dr. Alfred Adson, of the Mayo Clinic, had successfully opened and drained an abscess in the pole of the right frontal lobe. Two years later she began to have convulsive seizures, which started with upward deviation of the eyes, turning of the head to the left and pain in the right frontal region of the head, followed by a generalized convulsion.

Physical Examination.—The results were essentially normal, and a pneumoencephalogram showed enlargement forward of the anterior horn of the right lateral ventricle.

Operation.—A scar was observed to pass from the skull defect downward into the right frontal lobe, the track of the former abscess. There was atrophy of the cerebral tissue around this core, and several bits of connective tissue passed into the surrounding frontal pole. A cylinder of brain, about 4 cm. in diameter, including the anterior end of the ventricle, was excised. There has been no attack during the five and a half years since operation.

Histologic Observations.—In this case, as in the other examples of this type of meningocerebral cicatrix, the features already described in case 1 were to be seen. The central portion of the scar was made up of piloid glia, connective tissue and scattered large vessels. This was surrounded by gray matter containing normal ganglion cells. Between the scar and the gray mantle there were islands of gray matter, like those illustrated in figure 13.

In the scar there were occasional small patches of phagocytes and small cysts, suggesting progressive destruction, as well as a few polymorphonuclear leukocytes. At occasional points in the intermediary zone also there were pyknosis of nerve

cells, chronic and acute degenerative forms of neuroglia cells and patches of macrophages. The blood vessels in the central scar were large and thick walled, but they lacked small branches almost completely. There were a marked increase in the number of such branches in the islands of gray matter and an enormous increase in the more distant gray matter of the cortex.

CASE 3.—*Atrophy and adhesions, postmeningitic.*

History.—J. D., a man aged 30, complained of epileptic seizures. At 6 months of age he had had a febrile illness, which left him with left hemiplegia. Seizures began at the age of 16 years.

Examination.—The patient appeared intelligent. He had left hemiparesis, and the left extremities were small and had imperfect cortical sensation. Pneumo-

Fig. 6 (case 3).—Photograph of the right cerebral hemisphere exposed at operation, showing result of infantile meningitis thirty years earlier.

encephalograms showed that the right lateral ventricle was enlarged and the septum pellucidum deviated to the right.

Operation.—Dense adhesions containing blood vessels united the dura and the pia. The pia was thickened everywhere; the convolutions were irregularly atrophied. Posteriorly there was a large round area in which fluid and gelatinoid scar replaced the brain tissue down to the ventricle. In figure 6 the area is indicated by the instrument. It was obvious that at the age of 6 months the patient had suffered from purulent meningitis, which had caused the destruction and adhesions. The area was excised. That it was a focus (not the only focus) for seizures is indicated by the fact that, although the patient has had a few attacks at long intervals since operation, the character of onset of these seizures has altered.

Histologic Observations.—There was a great deal of piloid gliosis, and many smaller and larger cysts were scattered through the tissue. In some places the

gliosis was loose and acellular, as though it was breaking down to form more cysts. There were islands of gray matter, and often a large vessel was present at the center of the island. There were only a few sheaves of piloid fibrils. In one section the gray mantle was "thinned out" until all ganglion cells disappeared. In this case progressive cell destruction was taking place, twenty-nine years after the meningitis, and the tiny foci of dying cells were most frequent in the zone between the gray and the white matter.

CASE 4.—*Focal microgyria.*

History.—W. K., a youth aged 18, had complained of seizures for three years. Birth had been difficult; there was marked cyanosis, and intracranial hemorrhage was suspected. Seizures began at the age of 15 years, characterized by an epigastric aura and followed by turning to the left and unconsciousness.

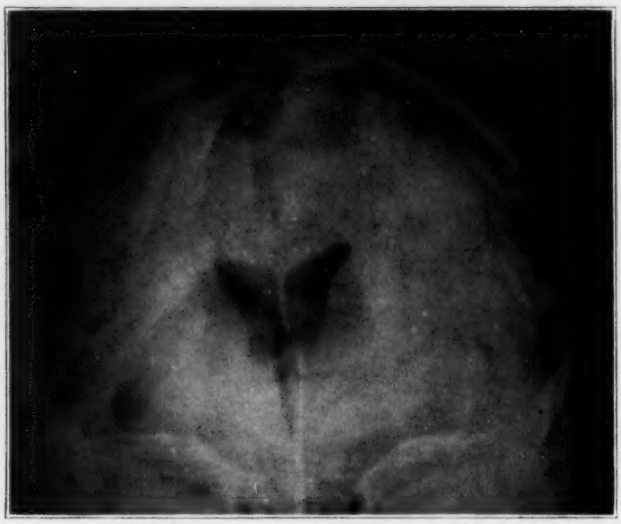

Fig. 7 (case 4).—Pneumoencephalogram taken with the brow up, showing small right cranial vault.

Examination.—The head was somewhat flattened on the right side, and roentgenograms showed the right cranial chamber to be smaller than the left (fig. 7). There was enlargement of the posterior end of the right lateral ventricle and right inferior horn.

Operation.—A right posterior osteoplastic craniotomy was carried out. Numerous filamentous adhesions were present between the dura and the pia, but they did not contain blood vessels, as do the adhesions caused by laceration or infection. These were the adhesions which are characteristically produced by an old, absorbed subdural hematoma. The convolutions of the temporal lobe showed the usual type of atrophy produced by hematomas at any time. That is to say, there was widening of the intergyral fissures, with little actual narrowing of the gyri, which were hard on palpation.

In the posterior parietal region there was atrophy of quite a different type. In a fairly discrete zone there was a group of gyri of about one-third the normal width. Here the attacks seemed to originate, so the zone was resected in a block, the

ventricle being opened. Because of return of attacks at the end of eighteen months, a more posterior osteoplastic opening was made and a second area of focal microgyria exposed and excised. This zone gave undoubted electrographic evidence of epileptogenic activity.

Histologic Observations.—In figure 8 one of the sections through an area of microgyria is schematized. Normal gyri are seen on either side. The two central gyri are so small that they might almost have disappeared from view. In these small gyri the gray mantle was represented only by islands of thinned-out ganglion cells, together with astrocytes, oligodendrocytes and nerve fibers. Even within the islands there were acellular patches. A vessel was observed at the center of almost half the islands, as may be seen in figure 13 (case 6).

In general, of course, the normal gray matter had the most voluminous vascular bed (upper panel, fig. 9), and the area of gliosis in which nerve tissue was practically absent contained larger vessels, which were at least as numerous as normal, but extremely few small branches of capillary and precapillary size (lowest panel, fig. 9). The middle panel of figure 9 shows on the left the vascular tree of

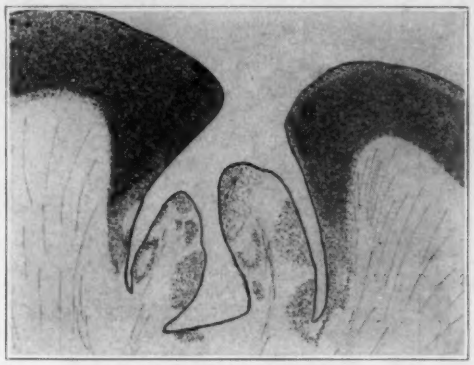

Fig. 8 (case 4).—Focal microgyria. Schematic cross section to show two small gyri, containing islands of thinned-out gray matter.

an island of gray matter and on the right the sudden reduction of vessels in the tissue adjacent to the island.

Study of astrocytes in different areas yielded much information as to past events. In the gray matter these cells were normally star shaped and of protoplasmic type. In the islands and thin zones of gray matter they tended to become fibrous and to multiply. At the periphery of such areas of gray matter chronic degenerative cells, Nissl's plump astrocytes and giant astrocytes sometimes appeared. In the neighboring aganglionic tissue these cells gave way to piloid astrocytes, the small neuroglia fibrils of which formed a glial network. In certain zones of maximum shrinkage, the fibrils of these piloid cells were condensed and gathered together in sheaves and whorls (fig. 10). The condensation of these fibrils into faggots would seem to be the result of shriveling of the tissue, in which all other cells except these hardy neuroglia cells have died. But even these fibrils eventually succumbed and liquified into small cysts, as shown in the upper left corner of figure 10.

In general, the astrocytes showed that in the normal gray matter there was no evidence of toxic or inflammatory influence and no ischemia which would otherwise have produced gliosis there. In the intermediary zone, however, between the normal tissue and the aganglionic scar, there were reactive and chronic degenerative changes of all types. In addition to this, there were scattered zones in which astrocytes had succumbed to acute degenerative change, such as results from complete ischemia, i. e., clasmatodendrosis (fig. 11).

Oligodendrocytes in the gray mantle at a little distance from the small gyri appeared normal, and the same was true of those in the adjacent white matter. In scattered patches, however, these cells showed acute swelling. These patches were

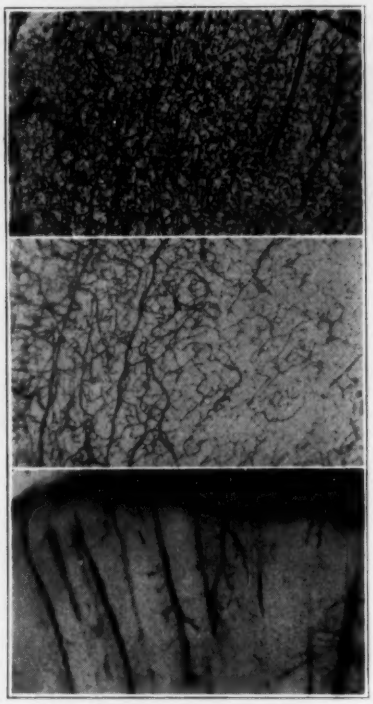

Fig. 9 (case 4).—Benzidine stain showing vascular tree. Above, normal gray matter; middle panel, island of gray matter in an atrophied gyrus, and below, aganglionic zone of piloid gliosis. Note the decreasing number of capillary and precapillary branches.

sometimes deep in white matter; more often, however, they occurred at the junction of atrophic gray and white matter and here the patches were often perivascular.

Still more significant is the fact that the microglia in these patches was also altered and the fat-filled phagocytes bore testimony to the fact that in that zone tissue had recently been destroyed. The evidence indicated that ischemia had been present in these patches, such as would be produced if the vessels in that area were

shut off. The end result of the continuance of destruction in such small areas would obviously be to make the gray matter progressively thinner and eventually disappear.

The history and the operative observations in this case make it obvious that there was damage to the brain at birth, leaving evidence

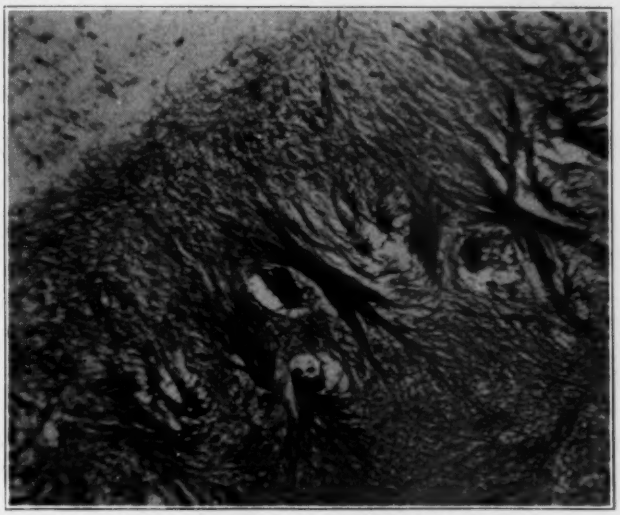

Fig. 10 (case 4).—Piloid gliosis in the aganglionic zone of a small gyrus. Note condensation of fibrils into faggots near the cyst in the upper left corner.

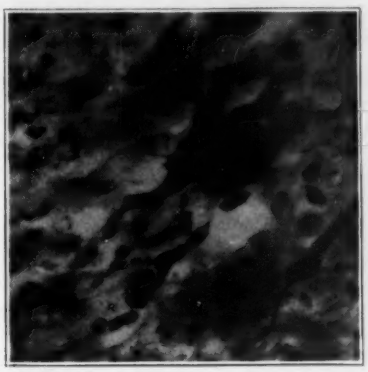

Fig. 11 (case 4).—Clasmatodendrosis of an astrocyte in a small area of destruction in the intermediate zone.

of subdural hematoma and areas of microgyria. The whole cranial cavity was small on the right side, suggesting that the total hemispheric volume was small during growth. The small gyri were pushed together by large gyri. This must have taken place during growth of the head;

consequently, the major atrophy of these small gyri occurred very early in life. Ischemia severe enough to destroy neurons evidently occurred, leaving only neuroglia in the small gyri. This ischemia doubtless occurred at the time of birth.

There was present, however, evidence of progressive destruction of cerebral tissue also. This destruction appeared in scattered patches that suggested strongly a relationship to blood vessels. On the other hand, in many of the islands of gray matter there was a vessel at the center, suggesting that the preservation of that bit of gray matter was due to the presence of the vessel direct from the pia, which resulted in a higher pressure of blood in the precapillaries near the vessel. Evidently these island vessels did not close, but the small areas of destruction must have been due to closure of very small vessels

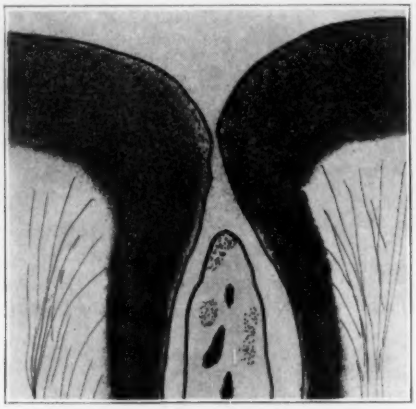

Fig. 12 (case 5).—Focal microgyria. Schematic cross section to show single small gyrus.

which lay in the intermediary zone between the area of gliosis and the normal convolution.

CASE 5.—*Focal microgyria.*

History.—G. A., a girl aged 16 years, complained of epileptic seizures. Her birth had been difficult, and she was said to have been markedly cyanosed as the result of compression of the umbilical cord about her neck. At 2 weeks of age there were several days of almost continuous seizures. After this development was slow but normal, and she was a little slow in using the left arm and leg. In time she seemed normal, both in school and in athletic activities. At the age of 10, seizures began. Her attacks at different times were of three different types, which seemed clearly related to lesions found in three different areas of the right hemisphere.

Physical Examination.—The results were normal except for comparative smallness of the arm, chest and leg on the left side and loss of two point sense in that arm and leg. Pneumoencephalography showed the right cranial chamber to be

smaller than the left and the posterior portion of the right lateral ventricle to be moderately enlarged.

Operation.—Extensive osteoplastic craniotomy showed no adhesions between the dura and the pia, which fact excludes subdural bleeding at birth. There was no yellowing of the pia-arachnoid. However, in certain areas the leptomeninges were white and opaque, and the subarachnoid space was deeper than usual. Beneath these thickened areas, in the upper postcentral, lower postcentral and lower frontal regions, were extremely small gyri. The postcentral gyrus was shrunken to a width of a few millmeters throughout its length, and it actually disappeared below the surface (fig. 12) in its midportion, appearing near the falx and below, near the fissure of Sylvius, in the areas of arachnoid thickening. The gyri adjacent to it were of normal width and appearance. Several similar gyri were observed in the frontal area.

These gyri were dissected out almost completely. They were made up of tough, yellowish tissue. The fact that the patient has had no seizures in the eighteen months since operation suggests that these useless convolutions were in fact epileptogenic foci. The smallness of the left side of the body and extremities was caused by the postcentral involvement, as has been pointed out elsewhere by Penfield and Robertson.[3]

Histologic Observations.—The convolutions were observed to have been converted into tough piloid glial tissue. The neuroglia fibrils were long and fine, and in places were condensed into sheaves, which seemed to have squeezed out the nuclei in the general process of shrinkage. Only an incomplete and much thinned mantle of cortical neurons remained. There were occasional evidences of destruction still progressing, as in case 4.

CASE 6.—*Focal microgyria.*

History.—N. I., a youth aged 16, complained of epileptic seizures. There was evidence of injury at birth. His twin brother was born dead. He nursed poorly and developed slowly, walking when 1½ years old and talking at the age of 2 years. After that he seemed to develop normally. At 18 months of age he had a fever and several convulsions. At the age of 7 years seizures reappeared and became hibitual. Each attack began with a peculiar sensation in his arm.

Physical Examination.—The results were essentially normal. The left cranial chamber was smaller than the right, as shown by the position of the falx and septum pellucidum in the roentgenograms. The left lateral ventricle was a little larger than the right posteriorly.

Operation.—Left osteoplastic craniotomy was carried out, and electrical exploration showed the central fissure to be several centimeters posterior to its expected position. Posterior to the postcentral gyrus and situated largely in the sagittal fissure was a collection of gyri not more than one-third the width of normal gyri. This area of closely packed, narrow gyri was excised, and there have not been any further seizures during the twelve months since operation.

Histologic Examination.—The small gyri contained many areas in which the gray mantle was narrow (fig. 13, upper panel), and in other areas only islands of gray matter remained (fig. 13, lower panel). As will be noted in the figure, these islands often contained a large vessel passing down from the pia, the preserved gray matter accompanying the vessel from the surface like a thick sleeve

3. Penfield, W., and Robertson, J.: Growth Asymmetry in Relation to Cicatricial Cortical Lesions, 1939, to be published.

about a tube. There were scattered small zones of cell destruction, usually about a capillary, and generally placed between the gray and the white zone so as to decrease progressively the width of the gray mantle. There were large areas of necrosis forming small cysts, as in the upper panel of figure 13, and fat-filled macrophages occurred here and occasionally in the tissue. Areas of piloid gliosis, replacing cerebral tissue, were numerous, and sheaves of fibrils occurred, such as are seen in figure 10.

CASE 7.—*Focal cerebral atrophy secondary to prenatal arterial occlusion.*

History.—A. M., a woman aged 25, complained of epileptic seizures, which dated from the age of 10 years. She had been cyanotic at birth, but breathed easily and fed well. At the age of 1 week, her mother noticed that the infant's

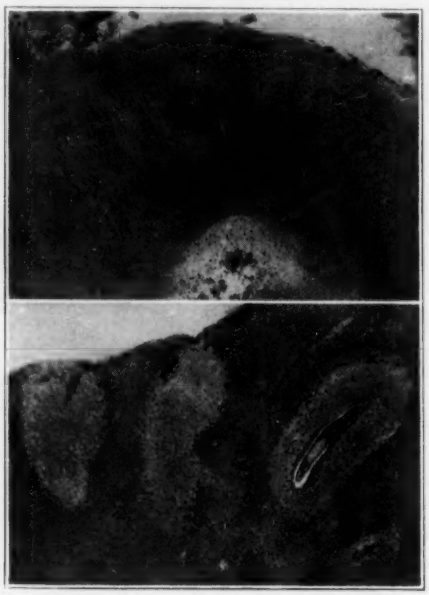

Fig. 13 (case 6).—Focal microgyria. Upper panel, thinned-out gray mantle; lower panel, islands of gray matter.

arm and wrist were held flexed and that the arm seemed paralyzed. At 2 months, the right leg was observed to be weak and the right arm and leg to be smaller than the left.

Physical Examination.—The patient had right incomplete hemiplegia and smallness of the right extremities. Her mentality was moderately reduced, but she was useful and happy in her family. The skull was flattened and small on the left side, and the left hemisphere was reduced in size, while the midportion of the ventricle on that side was enormously enlarged. The seizures began with a peculiar sensation in the right hand, which spread through the right side. This was followed by violent shaking of the paretic extremities, the head turning to the right, and loss of consciousness.

Operation.—There were no adhesions between the dura and the brain aside from the pacchionian granulations, which were observed to be farther from the midline than usual. There was nothing to suggest a previous hemorrhage.

The brain appeared normal anteriorly and posteriorly, but in the region where the fissure of Sylvius should have been the brain substance was replaced by a wide gutter of altered tissue, containing one small cyst. This altered tissue extended upward and backward from the position of the fissure to the falx. Outside this zone the gyri appeared normal.

The upward extension of the cerebral lesion was bordered anteriorly by narrow, abnormal convolutions, which were proved by stimulation to be the rolandic gyri. These gyri, together with the cicatricial tissue, were removed entirely with deep brain sutures and blunt dissection. It was evident that there was no middle cerebral artery, although the scar itself had pulsated actively before its removal and numerous arteries were encountered. That the tissue was functionally useless and contained the epileptogenic focus or foci is suggested by the fact that the operation resulted in no loss of function and the patient has remained free of attacks for two years, to the present.

Histologic Examination.—The block of excised tissue, cut across after fixation, is seen in figure 14. The larger convolutions may be seen on either side, and

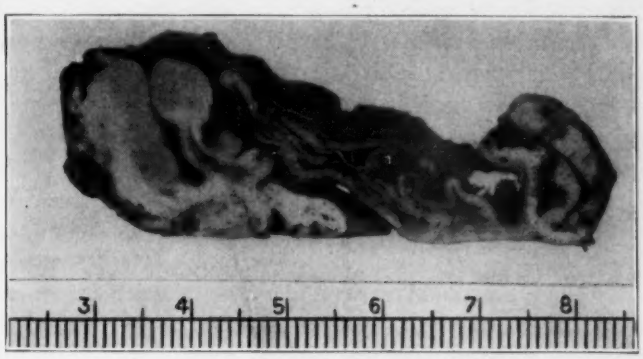

Fig. 14 (case 7).—Focal cerebral atrophy. Cross section of excised cerebral cyst.

the floor and roof of the cyst, in the center. Histologically, the roof of the cyst was made up of pia, with a thin layer of nerve cells beneath. These nerve cells disappeared at times, being replaced by an area of piloid gliosis. Toward the periphery the tissue was thicker; more ganglion cells were present, and the zone passed over abruptly into a normal convolution. In the thinned tissue there was much resemblance to the microgyria described in cases 4, 5 and 6, for there were small islands of gray matter, sometimes with a large vessel at the center of each island. There were many sheaves of piloid fibrils, especially just beneath the pia. Collagen was more abundant in these zones in this than in other cases.

In this case, twenty-five years after occlusion of the middle cerebral artery, destruction was still progressive, as shown by clasmatodendrosis of astrocytes and the appearance of fat-filled phagocytes. This patchy cell death was taking place especially beneath the gray mantle, i. e., between the gray and the white zone.

COMMENT

In this paper is reported a microscopic study of the focal cerebral lesions removed at operation from patients who suffered from epilepsy. In all, 95 such specimens, exclusive of neoplasms, have been included

in the analysis. The evidence that the lesion was epileptogenic varied from case to case. The clinical pattern of the attack, the history, the encephalogram, the objective evidence from inspection of the brain and the result of electrical stimulation under local anesthesia, all these elements entered into the conclusion reached at the operating table that the tissue removed was the originating focus of the patient's attacks. More recently, electrographic evidence has been added that the area in question was continuously giving rise to electric potentials typical of those encountered in an epileptogenic zone. The best evidence that the lesion removed was the actual focus was postoperative freedom from seizures or alteration of the seizure pattern.

Among the causes of these focal cerebral lesions were cerebral laceration, arterial occlusion, temporary ischemia, healed abscess and meningitis. Subdural hematoma and concussion were significantly absent from the list of causes.

Meningocerebral Cicatrix.—This may be produced by cerebral laceration due to penetration of the dura, to an abscess of the brain that has been drained and healed or to healed meningitis. The adhesions between dura and pia or dura and brain are dense and carry with them blood vessels. The central area of scar is gelatinoid in appearance, is tenacious and is capable of exerting an actual pull on the rest of the brain. Within this tissue no ganglion cells are to be found, and few if any nerve fibers. The tissue of the central cicatrix is made up of neuroglia cells of the piloid variety, the long slender fibrils of which form a network into which there is penetration from above of connective tissue with collagen fibers and blood vessels. Between this scar and the adjacent normal cortex lies an intermediary zone where gray matter is thinned out or is represented by isolated islands of ganglion cells surrounded by piloid glia cells.

Focal Microgyria.—This is produced by localized ischemia during birth. The clinical aspects of this condition are described in more detail elsewhere.[4] It seems evident that the combination of cranial compression and molding and defective fetal circulation results in ischemia of one gyrus or a group of gyri. In such gyri there is destruction of the nerve cells, which can survive complete anoxemia for only a few minutes. There results rapid convolutional shrinkage during the first year of life, the period of maximum growth of the brain. The normal convolutions are forced to move toward the area in question, and the cranial chamber, which enlarges only in response to the thrust of the brain, remains smaller on the affected side, while the underlying ventricle is molded into a normal general outline.

4. Penfield, W., and Keith, H.: Focal Epileptogenic Lesions of Birth and Infancy, 1939, to be published.

The tissue of the small gyri contains no nerve cells in some areas, but only piloid glial tissue. In the intermediate zone between this area and the normal cortex are islands of gray matter or atrophic extension of the gray mantle.

Brain Cysts.—Such cysts, large or small, may result from arterial occlusion. The cyst appears in the central area of complete destruction. There is an intermediate zone here too, between the cyst and the normal brain, where the ischemia was sufficient to destroy some of the nerve cells and where replacement by neuroglia has taken place. This produces small atrophic gyri in this zone.

Progressive Destruction.—This has been observed in all the epileptogenic lesions, however long the time that had elapsed since the original pathologic process, even ten to thirty years. It is not diffuse, but occurs in such small patches that it would seem to be perivascular. Actually, a small vessel is often to be seen at the center of such a patch, but the vessels show no objective evidence of thrombosis or closure. Acute swelling of oligodendrocytes and clasmatodendrosis of astrocytes, which are observed in these perivascular patches, constitute the acute degenerative change which these cells show when subjected to ischemia. The fat-filled phagocytes bear testimony that the process is producing cell death and myelin degeneration.

The distribution of the scattered patches of degeneration is constant in the lesions of various types. It lies in the intermediate zone, particularly at the lower margin of the gray matter or around the periphery of gray islands. It may also appear to some extent all through the central area of intense gliosis, where small cysts may result.

Blood Vessels.—The vessels of the normal gyri possess many capillary and precapillary branches. In the intermediate zone these small branches are much reduced in number, while in the central zone of scar, which typically contains no ganglion cells and few, if any, nerve fibers, capillaries and precapillaries are greatly reduced in number. This disappearance of small branches is not due to decrease of the larger trunks, for actually the number of vessels penetrating the scar seems usually to be greater than normal. This may, in part, be the result of shrinking of tissue that occurs here, thus bringing the entering vessels closer together. Such a reduction of small vascular branches has been reported by Alexander and Putnam [5] in the focal lesions of multiple sclerosis. It may well be that the reduction in capillaries is only a secondary indicator of the reduced metabolic requirement of the tissue, for it is recognized that gray matter has a high metabolic rate as compared with white matter, and no doubt the scar makes a much lower demand for oxygen than either.

5. Alexander, L., and Putnam, T.: Pathological Alterations of Cerebral Vascular Patterns, A. Research Nerv. & Ment. Dis., Proc. **18**:471, 1937.

The large trunks without branches do not lose their blood volume even when their lateral branches disappear, for at the operating table the scar is apt to bleed more when incised than is the normal brain itself. These arteries must carry blood through the avascular scar to terminal anastomoses in the gray matter of the intermediate zone.

Islands of Gray Matter.—The islands in this zone usually form a sleeve about a large artery that enters from the pia. The island is well provided with small branches from the central artery. The nerve cells, protoplasmic astrocytes and satellite oligodendroglia cells at the center of these islands are normal in appearance, provided the island is large enough. Toward the insular periphery the neurons and astrocytes show evidence of chronic (if not acute) degeneration, and the oligodendrocytes disappear. The same general relationships apply to the thinned-out gray mantle, which may not have broken up into islands.

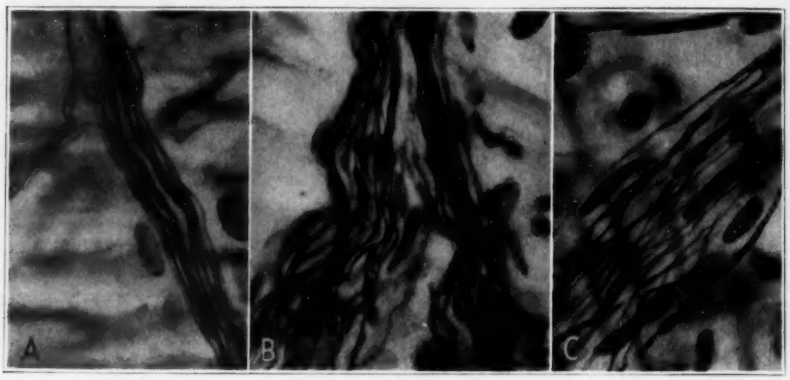

Fig. 15.—Perivascular nerves stained on cerebral cortical arteries, all approximately 100 microns in diameter and of the same magnification. *A*, artery from the normal part of the cortex of an epileptic patient; *B*, artery in the meningocerebral cicatrix in case 1; *C*, artery on a small gyrus in case 4.

Perivascular Nerve Plexuses.—The nerve plexuses on the vessels in the scar contain more fibers than those on vessels of the normal convolutions, although the appearance of the fibers is the same (fig. 15). The blood vessels themselves show no evidence of primary pathologic change, no thrombosis. The whole zone through which these arteries without branches pass gives evidence of spotty degeneration, which is often acute. These patches of destruction extend as far as the anastomosis of the arteries with those that enter through normal gray matter. The vessels show no evidence of thrombosis. It seems reasonable, therefore, to conclude that the perivascular destruction mentioned previously must be due to temporary closure, to vasoconstriction.

The gray matter of each island is apt to be normal near the central trunk of the vessel. This core of tissue has been protected from

ischemia, for its entire blood supply comes from the trunk in question. Only farther from the trunk does the tissue receive some of its ordinary blood supply from the anastomosing branches of the neighboring scar vessel. It might be argued further that these scar vessels carry to their terminal anastomoses a somewhat higher pressure of blood because of their lack of lateral trunk branches, and so gradually encroach on tissue formerly irrigated by vessels of normal complex structure.

CONCLUSION

We conclude that the arteries of an aganglionic scar undergo periodic positive constriction. This may be due to the abnormal scar tissue which surrounds the vessels. It may be due to the more voluminous perivascular plexus of the arteries of the scar. Or it may be that the lack of side branches subjects the arterial trunk to abnormal stretch stimuli. (Stretch seems to be an adequate stimulus for producing local constrictions of cerebral vessels, according to work by Echlin carried out in our clinic.) Such local irritability of the arteries of the central scar would produce the continuing destructive atrophy which is the universal histologic characteristic of epileptogenic lesions.

We are not in a position to say that such punctate destruction does not occur in scars which have not given rise to epileptic seizures. For the present we can only point out that this extremely slow, advancing destruction occurs at the frontier between the lesion and the functional cortex. This is the zone in which epileptic discharge seems to occur. This is the zone where electrical stimulation may reproduce a patient's habitual seizure. We are not suggesting that a spontaneous seizure results directly from widespread vasoconstriction in this zone. The invariable accompaniment of epileptic discharge is local vasodilatation, which begins shortly after the onset of the discharge.[6]

It is evident, however, that the scattered occasional vasoconstrictions that occur in this frontier zone produce progressive damage to scattered nerve cells. This phenomenon may well be an important mechanism in the charging process that periodically results in the explosive spreading discharge of ganglion cells that constitutes the physiologic basis of each recurring epileptic seizure.

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6. Gibbs, F. A.: Cerebral Blood Flow Preceding and Accompanying Experimental Convulsions, Arch. Neurol. & Psychiat. **30**:1003 (Nov.) 1933. Gibbs, F. A.; Lennox, W. G., and Gibbs, E. L.: Cerebral Blood Flow Preceding and Accompanying Epileptic Seizures in Man, ibid. **32**:257 (Aug.) 1934. Penfield, W.: The Circulation of the Epileptic Brain, A. Research Nerv. & Ment. Dis., Proc. **18**:605, 1937. Penfield, W.; von Santha, K., and Cipriani, A.: Cerebral Blood Flow During Induced Epileptiform Seizures in Animals and Man, J. Neurophysiol. **2**:257 (July) 1939.

DISCUSSION

DR. WILLIAM G. LENNOX: I think I can say for Dr. Cobb that all of those present who have any interest in the problem of epilepsy realize deeply their obligation to Dr. Penfield and his workers at the Montreal Neurological Institute both for this presentation and for many others which have come and which they know will come from those laboratories. To my rather fastidious mind there seems to be some contradiction in terms in speaking of an epileptogenic lesion. "Genic" means generative and implies birth. The surgeon, one knows, is able to deliver a living child from a body which is already dead, but even a surgeon of Dr. Penfield's ability cannot be expected to deliver a discharging nerve impulse from a dead neuron. Of course, the neurons which can be demonstrated as a part of the pathologic lesion are not functioning neurons and therefore cannot give rise to an epileptic discharge. If Dr. Fulton were here, he might be able to invent the proper Latin term for it, a term which would suggest an epileptic-assisting or epileptic-stimulating lesion.

If it were just the lesion itself that was important, one would ask the authors to demonstrate in what way histologically the lesions obtained from patients having seizures differ from lesions obtained from patients not subject to seizures.

It seems to me that this presentation is particularly valuable as pointing out the progressive nature of a lesion, the fact that it presumably may grow and grow for many years after the original injury was incurred. The question arises in my mind whether the authors would say, therefore, that the older a lesion is the larger it is, also perhaps that the larger a lesion is the more likely it is to be associated with epilepsy.

The third point which occurs to me is to question their interpretation of the circulatory phenomena. I rather take it that the evidence is circumstantial that the circulatory changes are related to the seizures themselves. The authors perhaps claim that these changes are related only to the progressive extension of the lesion.

A month or so ago, Dr. Erickson, from the same clinic, read an interesting paper in Chicago and, I believe, showed that the circulatory changes which took place locally in a discharging area were associated with an increase rather than a decrease in blood flow.

Finally, I would ask a question for future answer: What is the relation of the lesions to the associated electroencephalographic abnormalities, and is success with operation conditioned by the amount of abnormal electrical activity which surrounds this area of trauma?

My colleagues and I have been rather discouraged to find that persons who have a history of a localized lesion and localized seizures also may have a good deal of scattered abnormality over the cortex; 1 or 2 of the patients on whom we had frontal lobectomy performed for localized electrical disturbance later on showed this electrical disturbance in other parts of the brain. That is, there seems to be a sort of metastatic functional activity which extends progressively even beyond the area of demonstrable damage.

DR. WILDER PENFIELD: Dr. Lennox has brought up a number of points in which we are much interested. I think the name "epileptogenic" may be open to question. The lesion that is removed is not a completely dead lesion; I wish it were. The lesion that is removed usually includes the frontier zone which has nerve cells which we believe are often under an abnormal influence. So that in this sense it was an active part of the brain, perhaps not functionally active in the usual meaning of the word "function," but active in the sense of continuing to produce periodic seizures.

Dr. Lennox brought up the question of whether, according to this connection, the older a lesion is the larger it is. I think our answer would be "yes," inasmuch as we have invariably found progressive destruction. That does not mean large areas of destruction; it does not mean anything that can be seen without the

microscope. These are tiny patches; they must advance very slowly. But I feel sure that over a period of years the atrophy about such an area must progressively increase.

Also, I wish to bring up and emphasize the fact that in concluding that there is a constriction of these arteries, which we believe to be vasospastic, we do not wish to assume that there is any specific constriction immediately preceding a seizure. That is a ghost that has been raised and laid many times. We do not propose to raise it again at this time. At least we have no evidence that there is any immediate constriction preceding any particular seizure but only that there is that zone in which tiny areas of progressive destruction are occurring, a zone which lies between the inert, the dead lesion (e. g., a scar), and the active brain. In this zone there are punctate areas of destruction around vessels, and the vessels appear normal. Therefore we are driven to the conclusion, just as Spielmeyer was in considering a rather different part of the brain, that those vessels close at times, close long enough to cause focal destruction.

It seems to me that we cannot, as Dr. Lennox pointed out, say anything more than that these focal constrictions occur in the zone of advancing atrophy. We cannot say that the process is the cause of the epileptic seizures, nor that it is the fundamental mechanism of the charging process that results in the occasional discharges of epilepsy. We may, however, adopt this as a hypothesis for further work.

He spoke of the question of the relationship of electroencephalographic evidence to the lesions. With the assistance of Dr. Jasper we have, in a fair number of cases, now carried out electroencephalographic examination on the exposed brain under local anesthesia; opening of the skull and of the dura may well have upset the stage for careful recording of the waves that were perhaps there before the operation was begun. We have found, of course, that the lesion itself is silent and that the edge of the lesion gives rise at times to spikes and often to delta waves. We have concluded that the more accurate way of getting close observation of the activity of the brain from an electroencephalographic point of view is to make a small trephine hole a few days before operation and to introduce one or more electrodes on the end of coated wires between the edge of the bone and the dura, bringing out the coated wires through a needle track in the scalp and putting on a dressing which leaves the wire outside. Then one can make an accurate study of the potentials of the brain over a period of a day or two before coming to a conclusion.

DR. STORER HUMPHREYS: At the present time we hope to carry out microscopic examinations of tissue located as accurately as possible, at the time of operation, to the point from which it is thought that the electrical potentials are coming. In this way we hope to connect a cytologic change with the electrical response of the brain.

ADJUSTMENT OF ACID-BASE BALANCE OF PATIENTS WITH PETIT MAL EPILEPSY TO OVERVENTILATION

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Overventilation is particularly effective in precipitating petit mal seizures, as has been pointed out by Gibbs, Lennox and Gibbs.[1] Only rarely in their experience has any other form of epileptic seizure resulted from vigorous overbreathing. From this one can conclude that rapid induction of respiratory alkalosis gives rise to a physicochemical state of the fluids bathing the nerve cells in the brain which is favorable for the appearance of the petit mal attack. One cannot say, however, whether this physicochemical state in patients with petit mal epilepsy is different from that obtaining in nonepileptic persons when they overbreathe or whether the nerve cells of the epileptic brain are abnormally sensitive to a change in acid-base equilibrium which is within normal limits. The present series of experiments were performed in an attempt to answer the first alternative. They comprise a study of the adjustment of the acid-base balance during and after overbreathing in a group of patients with petit mal epilepsy and a group of nonepileptic control subjects.

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* Rockefeller Traveling Fellow in Neurology.

This paper is no. XXXIII in a series entitled "Studies in Epilepsy."

Aid was received by the Department of Neurology at Harvard Medical School from the Rockefeller Foundation.

From the Laboratory of Physiology, Yale University School of Medicine; the Neurological Unit of the Boston City Hospital, and the Department of Neurology of Harvard Medical School.

1. Gibbs, E. L.; Lennox, W. G., and Gibbs, F. A.: Variations in Carbon Dioxide Content of the Blood in Epilepsy, Arch. Neurol. & Psychiat., this issue, p. 223.

METHOD

Blood was drawn from the internal jugular vein through a hollow needle as described by Myerson, Halloran and Hirsch.[2] Arterial blood was obtained by puncturing with a hollow needle any accessible artery, usually the radial. Samples were taken before, during and after a short period of voluntary hyperventilation. The carbon dioxide and oxygen contents of the blood were determined on 1 cc. aliquots by the manometric method of Van Slyke. The oxygen capacity was also measured.

The p_H of the blood samples was determined at room temperature as quickly as possible after being drawn. A glass electrode was used. The samples were tested in serial order, and the first measurements were rechecked at the end of the determinations. These rarely showed an acid drift greater than 0.015 p_H unit, indicating that glycolysis had not proceeded to an extent great enough to invalidate comparable results. The glass electrode was frequently standardized by a phosphate buffer made up to accord with the p_H scale proposed by Hitchcock and Taylor.[3] The p_H of all blood samples was corrected to 38 C. by assuming that a temperature coefficient of -0.013 p_H unit per degree is correct.[4]

The patients classified in this study as having petit mal epilepsy were those who had no history of any other type of seizure. Those classified as patients with grand mal had no history of any but grand mal attacks. Patients who had both grand and petit mal were classified as having a mixed type of epilepsy or as having both grand and petit mal. Three patients were studied who had psychomotor seizures, whether with or without grand mal is indicated in each case.

INITIAL p_H AND CARBON DIOXIDE TENSION

In figure 1 are plotted the initial values for the p_H of the internal jugular blood of all patients studied. It is seen that there is no significant difference in the initial p_H of the various groups. A boy aged 9 with petit mal epilepsy did have a slightly higher value than might be considered normal.

In figure 2 the initial values for the carbon dioxide tension of the internal jugular blood are plotted. These were estimated from the analytic data in conjunction with the nomograms of Van Slyke and Sendroy.[5] There appears to be no significant difference between the patients with petit mal epilepsy and the nonepileptic controls, with the exception of the boy aged 9, whose carbon dioxide tension of 36 mm.

2. Myerson, A.; Halloran, R. D., and Hirsch, H. L.: Technic for Obtaining Blood from Internal Jugular Vein and Internal Carotid Artery, Arch. Neurol. & Psychiat. **17**:807 (June) 1927.

3. Hitchcock, D. I., and Taylor, A. C.: The Standardization of Hydrogen Ion Determinations, J. Am. Chem. Soc. **60**:2710, 1938.

4. Nims, L. F.: Unpublished data.

5. Van Slyke, D. D., and Sendroy, J., Jr.: Line Charts for Graphic Calculations by the Henderson-Hasselbach Equation, and for Calculating Plasma Carbon Dioxide Content from Whole Blood Content, J. Biol. Chem. **79**:781, 1928.

was 11 mm. lower than the average value observed. The 3 patients with grand mal included in this series of observations had distinctly higher values for carbon dioxide tension than did the controls. A larger series might show that patients with petit mal and those with grand mal have differences in the p_H and in the carbon dioxide tension of the blood similar to the differences in carbon dioxide content previously reported.[1]

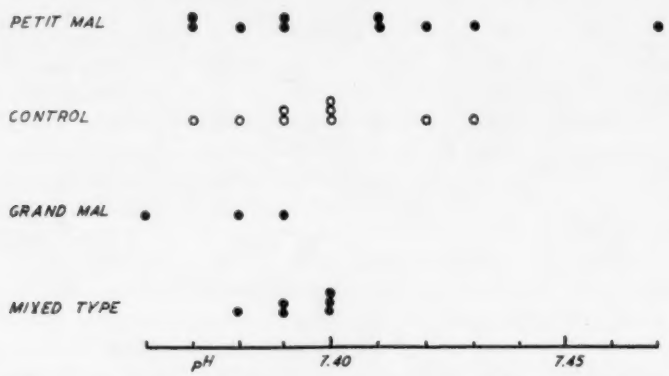

Fig. 1.—The p_H of the internal jugular blood of various patients.

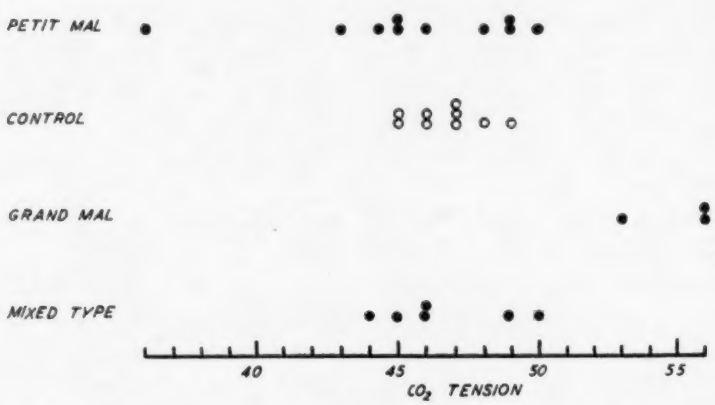

Fig. 2.—Carbon dioxide tension of the internal jugular blood of various patients.

CARBON DIOXIDE CONTENT

Overventilation usually produces a greater drop in the carbon dioxide content of the internal jugular blood in patients with petit mal epilepsy than in the control subjects. In addition, the carbon dioxide content of the blood of persons with epilepsy is prone to remain at low levels for some time and may show marked fluctuations in successive samples

before a return toward the initial values is evident. This fact is interesting in itself, as the seizure induced by overventilation may also occur some time after hyperpnea has ostensibly ceased. The magnitude of these differences is illustrated in figure 3, in which is plotted the time course of the carbon dioxide content of the internal jugular blood for a control subject and for a patient with petit mal epilepsy. The findings might be explained by simply assuming that the epileptic subject overbreathed to a greater extent than did the control, but the results obtained are so generally representative of the two groups studied that it is

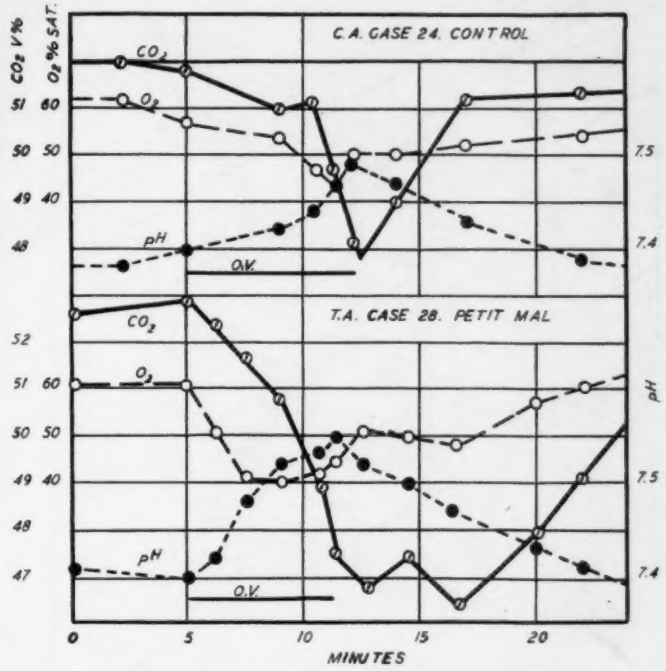

Fig. 3.—Comparison of the levels of carbon dioxide, oxygen and p_H of the internal jugular blood during and after overventilation in a normal control subject and in a patient with petit mal epilepsy.

believed that the time course of the carbon dioxide changes represent a fundamental distinction between the patient with petit mal epilepsy and the control subject.

ACID-BASE LOOPS

It is now generally recognized that the complete acid-base balance of the blood may be expressed in terms of the three variables—the concentration of base bicarbonate ($BHCO_3$)p, the carbon dioxide tension and the p_H, any one of which may be calculated if the other two are

known. The triaxial plot introduced by Shock and Hastings [6] furnishes a convenient method of visualizing the changes in acid-base balance that may take place. Such a plot is presented for a nonepileptic subject in figure 4. The shift from a starting position in this triaxial reference system will be referred to as the displacement path. The displacement path during overventilation is nearly a straight line, and during recovery

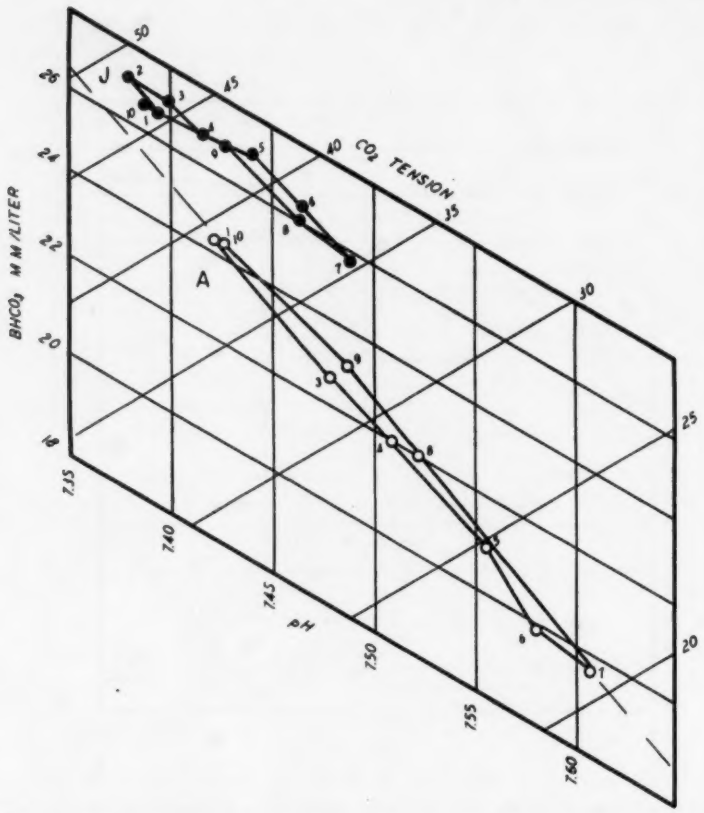

Fig. 4.—Displacement path for a nonepileptic control subject (C. A., case 24) during and after voluntary hyperventilation. *A*, with open circles, indicates acid-base loop for arterial blood; *J*, with solid dots, that for internal jugular blood. Arterial and venous samples were taken simultaneously. The numbers beside the points denote the order of the samples.

the path is retraced in both the venous (internal jugular) and the arterial (femoral) blood.

6. Shock, N. W., and Hastings, A. B.: Studies of the Acid-Base Balance of the Blood: III. Variation in the Acid-Base Balance of the Blood in Normal Individuals, J. Biol. Chem. **104**:585, 1934.

The displacement path for the arterial blood is parallel to the theoretic carbon dioxide absorption curve, as is indicated by the dotted extension of the displacement path in figure 4. This confirms the original observations of Shock and Hastings [7] on blood from the finger. However, the slope for the displacement path of the venous blood is markedly less, as is also the magnitude of the change in the various components, even though simultaneous samples are compared. This

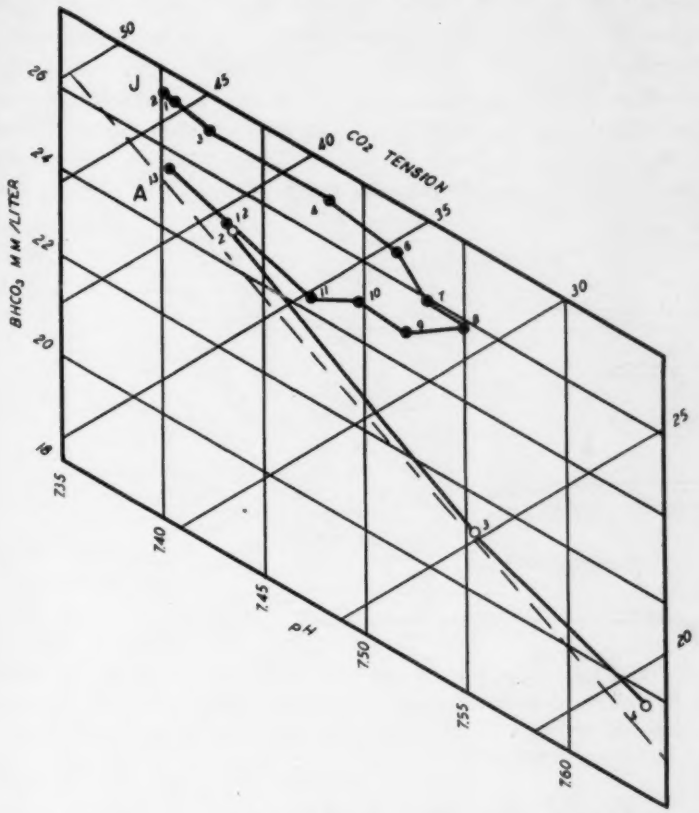

Fig. 5.—Displacement path for a patient with petit mal epilepsy (T. M., case 28) during and after overventilation. *A*, with open circles, indicates acid-base loop for arterial blood; *J*, with solid dots, that for internal jugular blood. Arterial and venous samples were taken simultaneously. The numbers beside the points denote the order of the samples.

difference illustrates the buffering capacity of the tissues involved, the brain in this instance. This apparent "buffer capacity" must depend on

7. Shock, N. W., and Hastings, A. B.: Studies of the Acid-Base Balance of the Blood: IV. Characterization and Interpretation of Displacement of the Acid-Base Balance, J. Biol. Chem. **112**:239, 1935.

several mechanisms, including blood flow, rate of metabolism and other active processes, in addition to the usual chemical buffer systems. These mechanisms may be thought of as control mechanisms, tending to maintain the physicochemical state of the brain somewhat independently of changes elsewhere in the body.

The displacement path for nonepileptic subjects is usually a loop of small area. This type of path is to be contrasted with that observed for a petit mal patient, in whom the general finding is a wide loop (fig. 5). The venous blood here shows a marked shift toward a fixed acid acidosis after overventilation. Shock and Hastings [7] have observed loops in finger blood in normal persons, with the change in the same direction as that indicated after overventilation. In comparing these results with

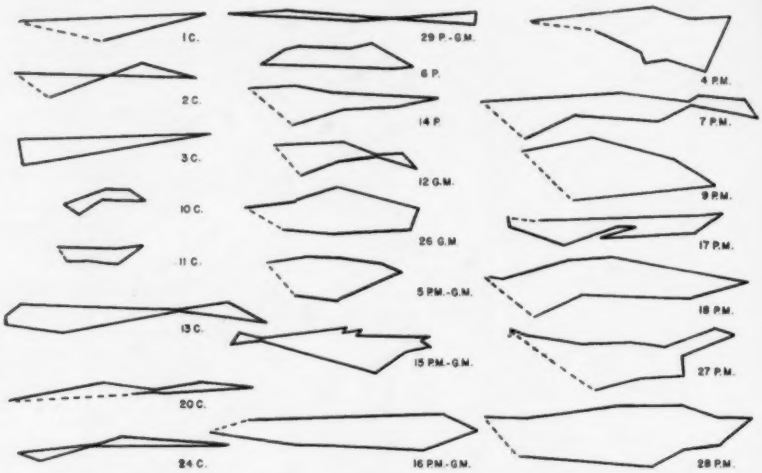

Fig. 6.—Acid-base loops for the internal jugular blood of various patients produced by voluntary overventilation. *C* indicates control subjects; *P*, patients with psychomotor epilepsy; *G. M.*, patients with grand mal epilepsy, and *P. M.*, patients with petit mal epilepsy.

theirs it should be remembered that there is little reason to suspect that blood from the finger and that from the internal jugular vein should behave in exactly the same manner. However, the response at the two sites is qualitatively similar. The aspect of the problem that is interesting in comparing the epileptic and the nonepileptic subject is the quantitative difference in the area of the loops.

The quantitative aspect is illustrated in figure 6, in which the loops obtained are arranged for comparison. All 10 patients with petit mal epilepsy have loops of greater area than do the 8 nonepileptic controls. The altered picture for internal jugular blood found in patients with

petit mal epilepsy during and after overventilation suggests that the physicochemical state of the fluids of the epileptic brain is different from that obtaining in the brain of the nonepileptic control subject.

CONCLUSIONS

The person with petit mal epilepsy responds to overventilation with a greater drop in the carbon dioxide content of the internal jugular blood and maintains the low level reached for a longer period after the overbreathing has ceased than does the nonepileptic control subject. The corresponding changes in the acid-base balance are such that the epileptic patient has an acid-base loop of greater area than the control subject. These findings can be explained on the assumption that the mechanisms which regulate the physicochemical state of the fluids of the brain are somewhat impaired in petit mal epilepsy, so that the person with such a condition is not able adequately to control or quickly adjust the acid-base balance when it is disturbed by overventilation.

PHYSIOLOGY OF CONCUSSION

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The animal studies described in this paper were undertaken to determine the mechanisms operating in sudden loss of consciousness following blows to the head. It was anticipated that such an investigation might help to explain the physiology of concussion. In this work emphasis was placed on the study of unconsciousness from simple concussion not associated with intracranial hemorrhage, cerebral laceration or other gross pathologic lesion.

A review of the literature concerning acute unconsciousness from blows on the head shows that there has been little recent investigation. However, many hypotheses have been set forth to explain this unconsciousness.

Cannon, in 1901,[1] investigating intracranial pressure following trauma to the head in anesthetized cats, reported that the immediate effect was a sudden increase in the intracranial pressure at the time the injury was received. The author, however, did not indicate the actual intracranial tension developed at the time of the blow. The only actual pressure values given were those taken after an interval sufficient for trephining the skull and inserting a cannula. At this time the intracranial pressure varied from 20 to 47 cm. of water. The normal pressure was 13 cm. of water. Cannon, in addition, reported falls in blood pressure at the time of the blow.

Wolff,[2] in 1936, indicated, among other things, that the usual sequel of a sudden increase in the intracranial pressure was loss of consciousness as a result of sudden cerebral anemia, but he failed to present evidence.

Cannon's evidence, together with several generalizations of others (Wolff,[2] Miller[3] and Wiggers[4]), indicates that there is some change

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From the Department of Physiology of the University of Chicago.

1. Cannon, W. B.: Cerebral Pressure Following Trauma, Am. J. Physiol. **6**:91 (Oct.) 1901.

2. Wolff, H. G.: The Cerebral Circulation, Physiol. Rev. **16**:545 (Oct.) 1936.

3. Miller, G. G.: Cerebral Concussion, Arch. Surg. **14**:891 (April) 1927.

4. Wiggers, C. J.: Physiology in Health and Disease, ed. 2, Philadelphia, Lea & Febiger, 1937, p. 816.

in intracranial pressure following a blow to the head. The purpose of the present work was to investigate thoroughly this problem along similar lines, recording actual pressures at the time of injury, and to attempt to correlate such pressures with loss of consciousness.

APPARATUS

On the premise that there is a change in the intracranial and the blood pressure concurrent with a blow causing unconsciousness, these pressure levels were recorded. When one attempts to record such pressures, difficulties arise in finding (1) a satisfactory method of immobilizing the animal's head, (2) a cannula which will allow free passage from the cerebrospinal fluid to the manometric system used, (3) a means of delivering a blow to the head and (4) a manometric system with little inertia.

A head holder, illustrated in figure 1, was constructed to immobilize the animal's head. It consisted of an adjustable, curved piece of black iron arching over the

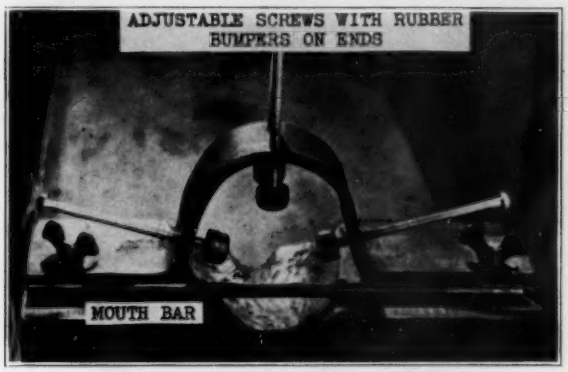

Fig. 1.—The head holder employed.

head; it held four machine screws with rubber bumpers on the ends. These could be screwed down tightly against the skull without causing injury to the skin. A mouth bar placed between the jaws prevented the head from being pulled back when the screws were down.

The cannula used is illustrated in figure 2 *B* (diagrammatic sketch, *A*). This cannula was devised after several misfortunes with an open end type formerly employed. It was constructed of a piece of 7/16 inch (11 mm.) hexagonal brass rod with a 5/16 inch (7.9 mm.) tapered thread cut on one end, the taper holding the cannula securely in the hole trephined in the skull. This threaded end was closed at the tip, and 1/16 inch (1.5 mm.) from the end a circular relief was cut. Ten small holes were then drilled in the relief into the central lumen of the cannula. A cannula of this type afforded a means of recording changes in intracranial pressure as it made it impossible for the brain to herniate against the holes at the sides and occlude them. This was not the case with the old type of open end cannula. Also illustrated in figure 2 *A* and *B* is the coupling connecting the cannula with the tubing of the manometric system. This coupling was added so that the cannula could be screwed into the skull while still con-

nected with this tube. With such a coupling no fluid is lost, and air bubbles are not introduced into the system.

Two methods of delivering a blow were used in this study. By the first method the blow was delivered by a padded, circular disk of steel attached to the end of a pipe, the pipe running in two horizontal sleeves. With this a blow of considerable force could be delivered to the side of the head. Some indication of the magnitude of the blow was given by a dynamometer mounted behind a second circular, padded disk. The second disk was attached to the rod running to the recording spring of the dynamometer, and was placed on the side of the head

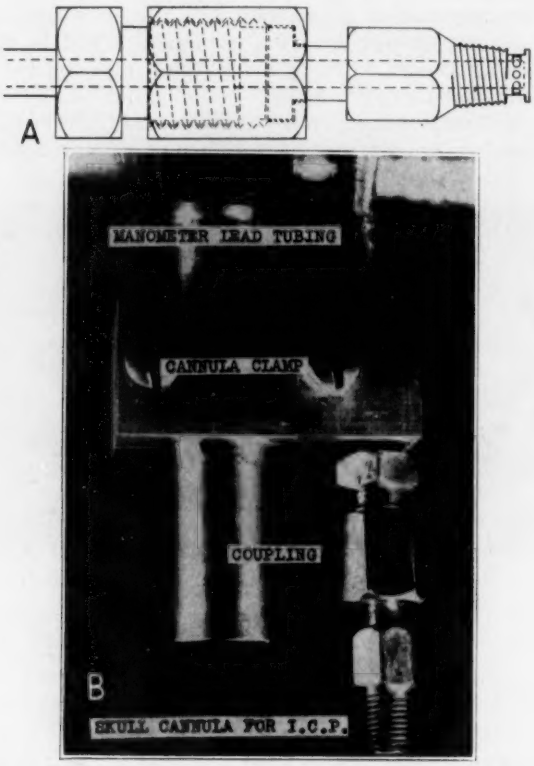

Fig. 2.—*A*, cross sectional drawing of skull cannula, showing small holes cut in circular relief, coupling and manometer tubing. *B*, skull cannula for recording intracranial pressure and coupling connecting the cannula with the manometer tubing. The heavy clamp is attached to a rigid wall bracket (fig. 3) and prevents artefacts due to vibration.

opposite the disk used to deliver the blow. The magnitude of the blow was read in kilograms.

The second method (illustrated in fig. 3) was better and much simpler. A falling weight (1,220 Gm.) was guided by a ½ inch (1.27 cm.) sleeve sliding on a vertical square bar suspended from the ceiling. The head holder and animal board could be moved under the vertical guide rod. The weight could be raised

to a desired height and held there by an adjustable catch and trigger arrangement mounted on the wall of the room.

The choice of a manometric system for recording intracranial pressure during a blow was a difficult one. Investigation showed that the mercury manometer possessed too much inertia and would not give true records of the actual height of the rise in pressure. A modified aneroid manometer was used, but was discarded because of several difficulties in recording and of errors in measurement.

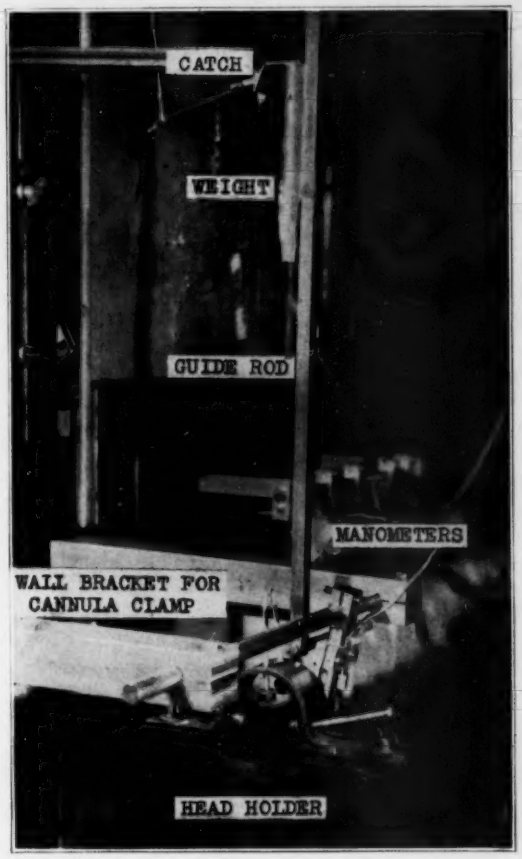

Fig. 3.—Mechanism for delivering a calculable blow, showing the weight held in readiness by the catch and the vertical rod for guiding the fall.

It was finally decided that the most useful manometric system was that of Hamilton,[5] with its optical system of recording. One addition to the standard apparatus was made. It consisted of a rigid wall bracket (fig. 3) and clamp

5. Hamilton, W. F.; Brewer, G., and Brotman, I.: Pressure Pulse Contours in the Intact Animal: I. Analytical Description of a New High-Frequency Hypodermic Manometer with Illustrative Curves of Simultaneous Arterial and Intracardiac Pressures, Am. J. Physiol. **107**:427 (Feb.) 1934.

(fig. 2*B*) which secured the lead tubing from the skull cannula and prevented artefacts due to vibration. This was satisfactory, as in all checks for artefacts, such as allowing the weight to drop on a block into which the skull cannula was screwed, practically no change in the manometric record was seen.

PROCEDURES

For clarity, the experiments reported may be divided into four series. In the first series dogs were anesthetized with ether (in a few instances, with paraldehyde and barbital), and the Hamilton apparatus was attached for recording the blood pressure and intracranial pressure. The intracranial pressure was taken with the cannula screwed into an opening in the parietal region of the skull, a round fault having first been made in the dura mater and cauterized. The blood pressure was recorded either from the carotid or from the femoral artery. Optical records were taken during the administration of a severe blow to the vertex of the animal. These blows were administered by the weight method already described.

In the second series the intracranial pressure was suddenly increased and immediately lowered to the normal level mechanically, rather than by delivery of a blow. A pressure bottle, connected in series with the skull cannula and manometric system, permitted rapid raising and lowering of the intracranial pressure. Series 2, 3 and 4 were performed with the ether removed for one and a half to two hours before recording, but with the incision thoroughly cocainized. In addition, a few experiments were carried out using preparations and apparatus of the same kind as those described for the second series, but the intracranial pressure was increased suddenly and repeatedly at two to three minute intervals. The mercury manometer was used mainly in series 2 and 3, in which the intracranial pressure was mechanically raised.

In the third series the intracranial pressure was raised in the conscious animal to levels below that of the blood pressure and maintained for a considerable time, all preparations for experiments having been made with the animal under ether anesthesia.

In the fourth series of experiments values for intracranial and blood pressures were recorded during the administration of a blow to the skull of sufficient force to cause unconsciousness. The criteria of unconsciousness will be described later in the paper. Here, as in series 1, the Hamilton manometer was used.

RESULTS

The results obtained in this study are reported in the order described under "Procedures." In the first series 14 dogs were used; a total of 25 blows were delivered. It was found that when the 1,220 Gm. weight was dropped on the head from an average height of 4 feet (121.9 cm.), with a calculated force of 50×10^6 dynes, there was invariably a sudden increase in intracranial pressure, amounting to an average of 300 mm. of mercury. The duration of the increase ranged from a minimum of one-fifth second in 1 case to a maximum of three-fifths second in another. In figures 4 and 5 are representative graphs for this group. The rise in intracranial pressure shown in figure 4 was 320 mm. of mercury; the rise shown in figure 5 was 240 mm. of mercury. Both increases were caused by the weight dropping from a height of 4 feet.

The effects on the blood pressure were not so consistent. Eight of the 14 dogs showed little or no fall in arterial pressure after blows. The record in figure 4 is typical of those in this series. In the remaining 6 dogs a fall in blood

pressure occurred. Figure 5 is representative of the magnitude and duration of the drop in blood pressure; the fall in this case was from 120 mm. of mercury systolic and 80 mm. diastolic to 80 mm. of mercury systolic and 55 mm. diastolic. At no time was a period of apnea observed after severe concussion, nor was there any striking change in respiratory rate or depth.

Postmortem examinations were made on all animals struck on the head. However, before the autopsy was begun samples of fluid taken by cisternal puncture

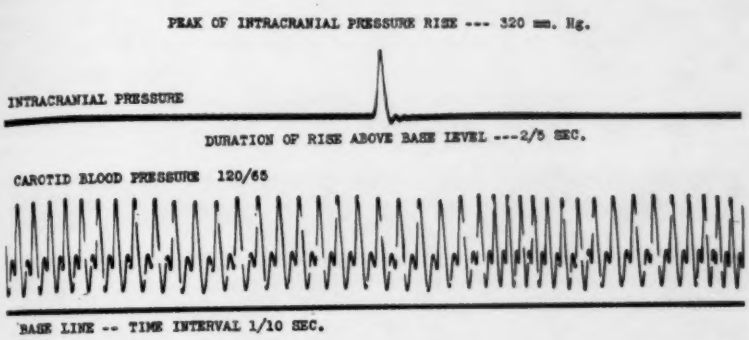

Fig. 4.—Optical manometric record of intracranial pressure and carotid blood pressure at the time of a blow to the vertex.

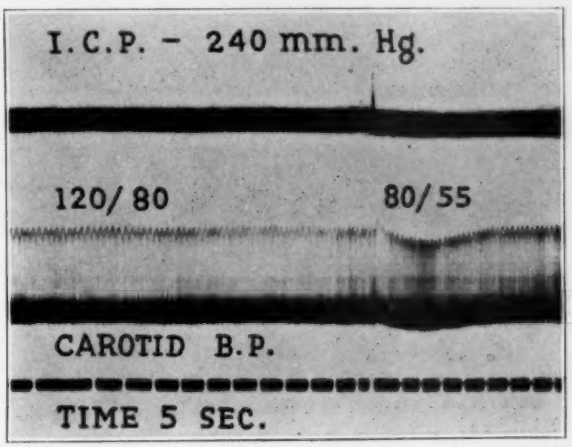

Fig. 5.—Optical record showing momentary rise in intracranial pressure and fall in blood pressure as the result of a blow. The tracings from above down represent the intracranial pressure, the carotid blood pressure and the time interval.

were examined for blood. The cerebrospinal fluid was clear. Next, after removal of the skull cannula, the calvarium was removed and the surface of the brain examined for petechiae, hemorrhage and similar lesions. Lastly, the brain was cut into ½ inch (1.27 cm.) frontal sections and examined. No changes were demonstrable.

The importance of this series is that in all cases observed the intracranial pressure at the time of the blow greatly exceeded the systolic blood pressure.

In the second series, in which the intracranial pressure of the conscious animal was raised mechanically, the results are significant. Invariably the animal lost consciousness when the intracranial pressure was suddenly raised to a level above that of the arterial blood pressure. Studies on 10 dogs are reported in this series. Figure 6 is a representative record. In this animal the intracranial pressure was suddenly raised to 230 mm. of mercury and immediately lowered to normal. The duration of the elevation in intracranial pressure above the blood pressure level was one second. This animal remained unconscious for five minutes. The duration of the loss of consciousness in the 10 dogs studied varied from a minimum of two minutes in 1 case to a maximum of ten minutes in another; the average was approximately five minutes. At no time was consciousness lost

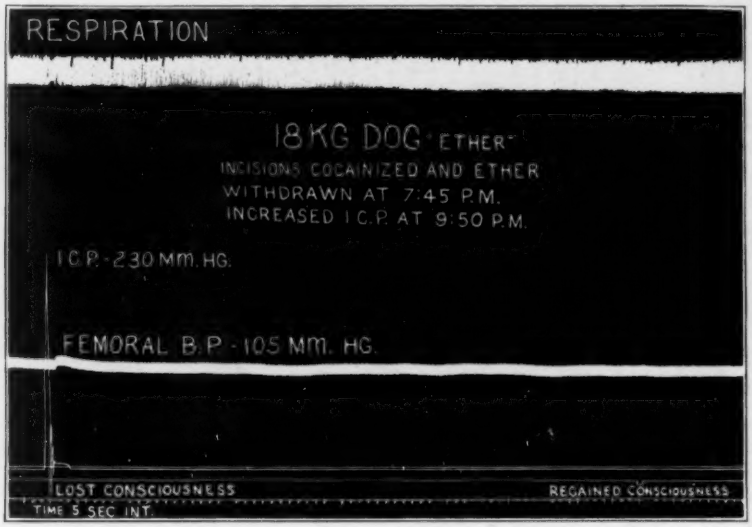

Fig. 6.—Representative record of the second series of experiments, in which the intracranial pressure was mechanically raised and immediately lowered to normal.

in these animals unless the intracranial pressure had exceeded the blood pressure. It is of note here that in 4 of the 10 animals loss of consciousness was preceded by rigidity of the legs, back and tail. This rigidity has been seen often on the football field when a player is knocked out, and has been reported to occur at times after a "knockout" blow in the prize ring.

Before concluding the report of results in the second series, it may be well to indicate how it was determined that the animals were unconscious. These animals could not be roused from their deep stupor by various stimuli, painful and otherwise; the pupils were constricted; the extremities were flaccid and did not move when noxious stimuli, such as pinching with a hemostat, were applied.

As indicated under "Procedures," a modification of the experiments in series 2 was carried out, using 4 dogs. The intracranial pressure was repeatedly increased before the animal was allowed to regain consciousness. These increases were

produced three times in succession, a two minute interval being allowed to elapse between each increase. The results were similar to those reported for the second series, but the period of unconsciousness following the last elevation in pressure was of longer duration than that produced by a single increase. The average duration of unconsciousness for series 2 was five minutes; the average following the last increase in intracranial pressure for these 4 dogs was eight minutes. No loss of consciousness occurred if these sudden, successive increases did not exceed the blood pressure.

In the third series the intracranial pressure was raised and held at a level just below the diastolic blood pressure; this pressure was maintained for intervals

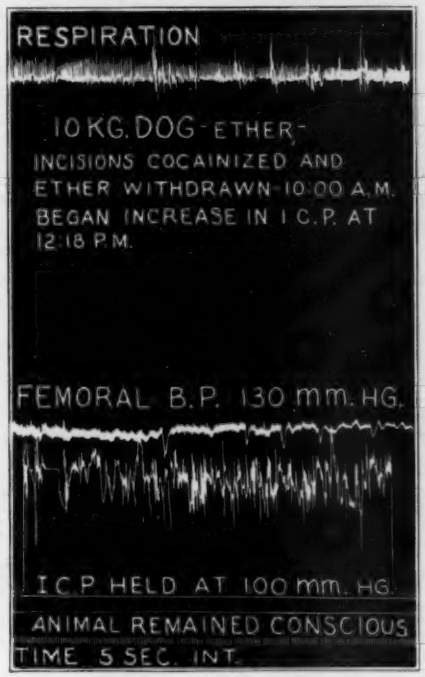

Fig. 7.—Tracings of respiration and blood pressure during a thirteen minute period of mechanically raised intracranial pressure, with the intracranial pressure maintained just below the arterial pressure (third series).

of five to thirty minutes. These experiments were made on conscious animals, previously prepared under ether anesthesia; 10 dogs were used. Figure 7 is representative of the records for this group. Unconsciousness was not seen in this animal when the intracranial pressure was held at 100 mm. of mercury for thirteen minutes. As indicated, this pressure was 30 mm. below the systolic blood pressure. Again, this brings out the point made in the preceding series, that loss of consciousness does not occur when the intracranial pressure level is below that of the arterial blood pressure.

Furthermore, the findings in the series just described help to clarify a question which is still being raised concerning the relationship of increased intracranial

pressure to medullary stimulation. It will be noted that there is little evidence of bulbar stimulation in figure 7 except occasional spasmodic breathing; the results for the remaining dogs in this series were similar. These observations confirm the early work of Cushing,[6] who indicated that bulbar stimulation did not occur until the intracranial pressure reached the level of the systolic blood pressure. On the other hand, there are still reports of cardiac slowing, elevation of blood pressure and respiratory changes when much lower levels of intracranial pressure were maintained for only a short time (Dixon and Halliburton[7] and Moore[8]).

Because of the nature of the fourth series of experiments, it was decided to limit their number. In 4 conscious preparations, a blow sufficient to cause unconsciousness produced changes in intracranial pressure comparable in magnitude and duration with those obtained in series 1. The average increase in intracranial pressure for the 4 animals was 327 mm. of mercury; individual values were 300, 250, 400 and 360 mm. of mercury. These levels had an average duration of two-fifths second. All 4 animals remained unconscious for about the same length of time; the average duration of unconsciousness was four and seventy-five hundredths minutes.

In spite of the limited number of experiments, the observations in this group are adequately correlated with those made in the first and the second series, and demonstrate that the period of unconsciousness produced by a blow to the head is identical in duration with that which occurs when the intracranial tension is suddenly elevated above the level of the arterial pressure without any complicating factors which might, theoretically, be present when the pressure is elevated by a blow to the head.

COMMENT

Cerebral concussion is one of the clinical entities the pathologic anatomy and physiology of which are poorly understood. It may be defined as a transitory period of unconsciousness as a result of a blow to the head from which complete recovery is the rule, if it is not associated with more serious injury to the brain. The period of coma is frequently of less than five minutes' duration. More prolonged periods of unconsciousness are almost always associated with evidence of cerebral contusion and laceration or intracerebral, subarachnoid, epidural or subdural hemorrhage or a combination of these.

The present work shows that a blow to the head sufficient to cause a brief period of unconsciousness in the dog, varying from two to ten minutes, but not to produce any intracranial hemorrhage or other pathologic alteration detectable with the naked eye, is invariably associated

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6. Cushing, H.: Some Experimental and Clinical Observations Concerning States of Increased Intracranial Tension (Mütter Lecture for 1901), Am. J. M. Sc. **124**:375 (Sept.) 1902.

7. Dixon, W. E., and Halliburton, W. D.: The Cerebro-Spinal Fluid: III. The General Effects of Increasing the Cerebro-Spinal Pressure, J. Physiol. **48**: 317 (July) 1914.

8. Moore, L. W.: The Effects of Increasing the Intracranial Pressure in Rabbits, Am. J. Physiol. **50**:352 (Dec.) 1919.

with an increase in the intracranial pressure considerably above the existing blood pressure level. These findings confirm those of Cannon,[1] but elaborate on them in that the intracranial pressure at the time of and immediately subsequent to the delivery of the blow to the head was measured. However, contrary to Cannon's report, it was found that the intracranial pressure, after the sudden transient rise, returned to its preexisting level. It seems likely that in the work of Cannon the blood which he saw beneath the dura mater after a blow was responsible for the prolonged rise in pressure of 47 cm. of water.

It is possible that the explanation of the rise in intracranial pressure is that offered by Cannon; i. e., the skull is indented by the blow and its volume thus reduced. Certain commonplace clinical observations, however, make this seem unlikely. It is a well established fact that a blow delivered by a pointed object or one of small diameter which produces a depressed fracture of the skull frequently does not result in loss of consciousness, whereas a severe blow in which there is no fracture, or only a linear one, almost always does. It appears likely, therefore, that deformation of the entire skull, thus reducing its volume, is more effective than a local indentation. It, of course, is a well established geometric fact that any distortion of a sphere rapidly and materially reduces its volume. Certainly, the calvarium, although rigid, possesses some degree of elasticity, particularly when subjected to a violent force.

Furthermore, it has been demonstrated that sudden, mechanical elevation of the intracranial pressure to a level comparable with that produced by a blow to the skull is sufficient to produce unconsciousness of similar duration in the dog, and that the increase in intracranial pressure is effective in this regard only when it is elevated to a level greater than the systolic blood pressure. In correlation of these observations, it has been shown that a blow delivered to the head of a conscious animal sufficient to elevate the intracranial tension to a level above the systolic blood pressure results in a period of unconsciousness identical with that produced by elevation of the intracranial pressure by other means.

In approximately one half of the experiments there was a fall in arterial blood pressure amounting to 20 to 40 mm. of mercury. The cases in which there was a fall are comparable with the case report by Cannon, in which there was a fall in arterial blood pressure from 135 to 95 mm. of mercury. It should be stressed, however, that unconsciousness from a blow occurred commonly when it was not associated with any fall in blood pressure.

In the interpretation of these results, the question arises as to whether unconsciousness can be explained on the basis of cerebral anemia. It

has been firmly established by Eyster and his associates[9] and Wolff[2] that the cerebral anemia resulting from increasing the intracranial pressure to a level above that of the blood pressure is complete, involving not only the superficial, but the deep, vessels of the brain. It necessarily follows, in the light of evidence presented here, that in the case of a blow on the head there is sudden, short lasting, complete anemia of the brain.

The question then arises as to whether this short lasting anemia is of sufficient duration to cause loss of consciousness. In support of the contention that it is, one may cite the work of Weiss and Baker.[10] These investigators showed that in some cases of hypersensitivity of the carotid sinus mechanism in man, severe pressure on the sinus produced immediate loss of consciousness. Of interest in connection with the production of unconsciousness is a quotation from their paper.

> It is not so much the absolute degree of alteration in the cerebral circulation as the rate (time element) of circulatory change that plays a fundamental etiologic role.

They further indicated that sudden ischemia may even be followed by hyperemia and yet produce unconsciousness. In addition, from the same study of Weiss and Baker, evidence is presented that syncope can occur without associated fall in blood pressure or cardiac slowing. This is in agreement with the observation in some of the cases reported in this paper that unconsciousness occurred without any fall in blood pressure or slowing of the heart.

Additional evidence in favor of cerebral anemia as the cause of unconsciousness was offered by Cannon.[1] The cases he reported are much like those described here, in that a fall in arterial blood pressure was in evidence after the blow. Cannon said:

> The readjustment of the circulation of the brain may be further hindered by the fall in arterial blood pressure immediately after trauma . . . Since there is in the brain at this same time a process of recovery from a checked blood flow (as a result of a sudden increase in intracranial pressure), the factors producing ordinary syncope are present.

Nevertheless, one cannot avoid the query: Can the stasis of blood for one fifth to three fifths of a second, with the resultant brief period of anoxemia, produce a period of cerebral inactivity (unconsciousness) of from two to ten minutes' duration? Or does this brief period of

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9. Eyster, J. A. E.; Burrows, M. T., and Essick, C. R.: Studies on Intracranial Pressure, J. Exper. Med. **11**:489 (May) 1909.

10. Weiss, S., and Baker, J. P.: The Carotid Sinus Reflex in Health and Disease: Its Role in the Causation of Fainting and Convulsions, Medicine **12**:297 (Sept.) 1933.

vascular compression and increased intravascular pressure result in a period of vascular disturbance—possibly vasoconstriction—which produces more prolonged stasis and anoxemia and thus accounts for the unconsciousness? At the moment, evidence is not sufficient to answer these questions.

In view of the available evidence, it is probable that the unconsciousness is due to cerebral anemia. The manner in which such anemia can produce unconsciousness is undetermined, though it may be through anoxia. According to Gerard,[11] loss of function, temporary or irreversible, most likely depends on the metabolic rates of various cells, the cells with a greater respiratory rate being the first to suffer from acute lack of oxygen. It has been firmly established, both directly and indirectly, that the respiratory rate of cortical tissue is considerably greater than that of peripheral nerve. Indirect estimations have been made by comparing the times of survival of function of different nerve tissues following deprivation of oxygen. On the basis of the survival times of twenty seconds for human brain and twenty minutes for peripheral mammalian nerve, it has been calculated that the respiratory rate of cortical tissue is sixty times that of nerve.[12] Although these rates are higher than those found by studies in vitro (the ratio of the rate for gray matter to that for nerve being 30: 1), some investigators believe that the latter are low.[12] Because the cortex has a high respiratory rate and is extremely susceptible to lack of oxygen, it is likely that brief periods of anoxemia are far more deleterious to it than to other tissues and that the anemia resulting from a blow to the head produces unconsciousness by anoxia.

As previously stated, it was hoped that animal experimentation might shed light on the *modus operandi* of concussion. One should consider in such an investigation the prize ring's "knockout" blow. It is generally agreed among fighters that it is easier to knock out an opponent by hitting a point on the lower jaw than any other on the head. However, although a more forceful blow appears to be needed, it is possible to knock an opponent unconscious with a blow to almost any region of the head. As to why a less forceful blow is required when it is delivered to the jaw one can only speculate; no animal experiments reported here or elsewhere involved such a blow.

In a discussion of the "knockout" blow it may be of interest to treat briefly the allied subject of the "punch-drunk" fighter; "punch drunk" is an epithet used to describe boxers who have received innumerable

11. Gerard, R. W.: The Metabolism of Brain and Nerve, in Luck, J. M.: Annual Review of Biochemistry, Stanford University, Calif., Stanford University Press, 1937, vol. 6, p. 419.

12. Gerard, R. W.: A. Research Nerv. & Ment. Dis., Proc., to be published.

blows during a lifetime of fighting. According to a number of investigators (Martland,[13] Carroll,[14] Parker,[15] Winterstein [16] and others), the term "punch drunk" recalls a number of definite symptoms, among which are included ataxia, impediment to speech, a vacant, staring look and some impairment of intelligence. As in the case of the "knockout" blow, many theories have been advanced to explain these symptoms. Such lesions as cell process fracture (Miller [3]) and perivascular hemorrhage (Parker [15]) have been advanced as explanations. Winterstein,[16] however, in a recent publication, stated that there are no histologic observations available to confirm the clinical findings.

It is possible that the work on concussion reported in this paper may help to explain the production of the syndrome "punch drunk." One wonders whether the irreparable damage to the central nervous system of some fighters may not be the result of many sudden anemias of short duration. The resultant periods of anoxia may act cumulatively in the production of tissue damage. A cumulative action of oxygen deficiency seems to be fairly well established in aviators ascending to high altitudes. Birley [17] indicated that aviators who frequently ascend to high altitudes find that their "ceilings" become progressively lower, and that this condition continues for months independent of additional ascents. Seibert [18] also reported cumulative effects of anoxia in pilots. If the pilot was allowed to ascend to a high altitude, loss of consciousness might result. Furthermore, in a recent symposium on anoxia it was indicated by Armstrong [19] that repeated exposures of rabbits to low oxygen tensions produced degenerative changes in the central nervous system. Again, a cumulative action was suggested. Obviously, these analogies are speculative. It is not assumed that the anoxia produced by a blow to the head is of the same order as that produced by brief exposures to high altitudes.

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13. Martland, H. S.: Punch Drunk, J. A. M. A. **91**:1103 (Oct. 13) 1928.

14. Carroll, E. J.: Punch Drunk, Am. J. M. Sc. **191**:706 (May) 1936.

15. Parker, H. L.: Traumatic Encephalopathy ("Punch Drunk") of Professional Pugilists, J. Neurol. & Psychopath. **15**:20 (July) 1934.

16. Winterstein, C. E.: Head Injuries Attributable to Boxing, Lancet **2**: 719 (Sept. 18) 1937.

17. Birley, J. L., cited by McFarland, R. A.: The Psychological Effects of Oxygen Deprivation (Anoxemia) on Human Behavior, Arch. Psychol., 1932, no. 145.

18. Seibert, E. G.: The Effects of High Altitudes upon the Efficiency of Aviators, Mil. Surgeon **42**:145 (Feb.) 1918.

19. Armstrong, H. G.: Toxicity of Oxygen at Decreased Barometric Pressures, Mil. Surgeon, to be published.

SUMMARY

Apparatus is described for recording in animals changes in intracranial pressure produced by a blow to the head.

The intracranial pressure, at the time of a blow of sufficient force to cause unconsciousness in the dog, rises to a height considerably above the systolic blood pressure. After the blow the intracranial pressure returns immediately to the normal level and remains there.

There is loss of consciousness in the dog when the intracranial pressure is mechanically raised to a level above that of the arterial blood pressure, although this pressure is maintained for only one second.

At no time is consciousness lost in the dog when the intracranial pressure does not exceed the systolic blood pressure, even though the lower pressure is maintained for long periods (thirty minutes).

Bulbar stimulation does not occur until the intracranial pressure reaches the level of the systolic blood pressure (Cushing).

There may or may not be a fall in arterial blood pressure after a blow to the head. The results in cases reported in which a fall was shown are in agreement with those reported by Cannon.

The loss of consciousness as a result of a blow on the head may possibly be explained on the basis of short lasting, complete cerebral anemia (Cannon). It is agreed with Weiss and Baker that the rate of circulatory change is important in the production of unconsciousness.

Hypotheses are advanced to explain the "knockout" blow of the prize ring and the allied condition, "punch drunk." The suggestion is made that the syndrome "punch drunk" may be the result of damage to the central nervous tissue from cumulative anoxia caused by repeated, short lasting anemias.

Dr. A. B. Luckhardt furnished guidance in this work; Dr. P. C. Bucy offered helpful criticism of the manuscript; Dr. C. C. Scott assisted in the laboratory, and Mr. A. Lutz helped in designing and constructing the apparatus.

THE SPINOTHALAMIC TRACT IN MAN

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In 1889 Edinger [1] described a tract taking origin from cells in or about the posterior horn, crossing the midline and ascending in the anterior or anterolateral column of the spinal cord. He was able to follow this column as high as the interolivary lamina, where it seemed to mingle with fibers of the medial lemniscus. Previous investigators had shown that fibers of the posterior root entered the posterior columns and ascended to the nuclei of the posterior columns in the medulla. Edinger noted that such a pathway could not explain the anesthesia (?) which he found on the contralateral side of experimental animals after hemisection of the spinal cord. He did not, however, recognize that there was not really anesthesia, but only analgesia. It was a clinician and neuropathologist who showed definitely that the fibers carrying pain and temperature reside in the anterolateral columns. Spiller [2] attended a patient suffering from generalized tuberculosis in whom there developed complete loss of appreciation of pain and temperature in the lower extremities with no diminution in the appreciation of tactile impulses. At autopsy, tubercles were observed in both anterolateral columns of the spinal cord in the lower thoracic region. Spiller therefore concluded that the fibers conveying pain and temperature sensibilities traverse the anterolateral columns. So convinced was he of the correctness of his conclusions that, seven years later, he referred a patient suffering severe pain from an inoperable tumor of the spine to Martin [3] for section of the anterolateral tracts. Thus, the first anterolateral chordotomy was performed, with gratifying results.

Knowledge concerning the function of the anterolateral column of the spinal cord has advanced rapidly as a result of examination in subsequent cases of anterolateral chordotomy. Because the majority of such

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1. Edinger, L.: Vergleichend-entwicklungsgeschichtliche und anatomische Studien im Bereiche des Centralnervensystems: II. Ueber die Fortsetzung der hinteren Rückenmarkswurzeln zum Gehirn, Anat. Anz. **4**:121-128, 1889.

2. Spiller, W. G.: The Location Within the Spinal Cord of the Fibers for Temperature and Pain Sensations, J. Nerv. & Ment. Dis. **32**:318-320, 1905.

3. Spiller, W. G., and Martin, E.: The Treatment of Persistent Pain of Organic Origin in the Lower Part of the Body by Division of the Anterolateral Column of the Spinal Cord, J. A. M. A. **58**:1489-1490 (May 18) 1912.

patients live for long periods after operation, anatomic studies of the degenerations following chordotomy rarely have been possible. Recently, I have had the opportunity to study the spinal cords and brains of 2 patients who died eighteen days and twelve weeks, respectively, after chordotomy.

The first of these cases represents an ideal anatomic experiment, and while the results in the second case are not as clearcut, they add confirmation to the findings in the first case.

HISTORICAL REVIEW

Several authors have studied the spinothalamic tract in lower animals. Quensel and Kohnstamm [4] (in rabbits), Mott [5] (in the monkey), Le Gros Clark [6] (in the monkey) and I [7] (in the monkey and chimpanzee) have followed the tract to the posterior part of the ventral nucleus of the thalamus. Le Gros Clark [6] and I [7a] suggested that there is probably a segmental distribution of its terminal fibers within the thalamus, those from the caudal spinal segments ending lateral to those from the higher segments. Choroschko [8] and Collier and Buzzard [9] traced degeneration to the caudal part of the ventral thalamic nucleus in cases of injury to the human spinal cord. Goldstein [10] gave an excellent description of the course and termination of the spinothalamic tract in man. More recently, Gagel examined the brains of patients on whom Foerster had performed anterolateral chordotomy, and traced the spinothalamic tract to the posterior part of the ventral nucleus of the thalamus.[11] Van Gehuchten,[12] with the Marchi technic, studied the

4. Quensel, F., and Kohnstamm, O.: Präparate mit aktiven Zelldegenerationen nach Hirnstammverletzung bei Kaninchen, Neurol. Centralbl. **26**:1138-1139, 1907.

5. Mott, F. W.: Experimental Inquiry upon the Afferent Tracts of the Central Nervous System of the Monkey, Brain **18**:1-20, 1895.

6. Clark, W. E. Le Gros: The Termination of the Ascending Tracts in the Thalamus of the Macaque Monkey, J. Anat. **71**:7-40, 1936.

7. Walker, A. E.: (*a*) The Thalamus of the Chimpanzee: I. Terminations of the Somatic Afferent Systems, Confinia neurol. **1**:99-127, 1938; (*b*) The Primate Thalamus, Chicago, University of Chicago Press, 1938.

8. Choroschko, W. K.: Sekundäre Degenerationen in aufsteigender Richtung bei Rückenmarksverletzungen, Monatschr. f. Psychol. u. Neurol. **26**:534-545, 1909.

9. Collier, J., and Buzzard, E. F.: The Degenerations Resulting from Lesions of Posterior Nerve Roots and from Transverse Lesions of the Spinal Cord in Man: A Study of Twenty Cases, Brain **26**:559-591, 1903.

10. Goldstein, K.: Ueber die aufsteigende Degeneration nach Querschnittsunterbrechung des Rückenmarks (Tractus spino-cerebellaris posterior, Tractus spino-olivaris, Tractus spino-thalamicus), Neurol. Centralbl. **29**:898-911, 1910.

11. Foerster, O., and Gagel, O.: Die Vorderseitenstrangdurchschneidung beim Menschen, Ztschr. f. d. ges. Neurol. u. Psychiat. **138**:1-92, 1932.

12. van Gehuchten, P.: Contribution à l'étude de la voie spino-thalamique chez l'homme, in Volume jubiláire en l'honneur du professeur G. Marinesco, Bucarest, Societé Roumaine de Neurologie, Psychiatrie et Endocrinologie, 1933, pp. 241-248.

course and termination of the spinothalamic tract in a patient who died fifteen days after complete transection of the spinal cord at the first dorsal vertebra. In none of these accounts of the spinothalamic tract in man has the termination of the tract been studied in detail.

METHODS OF STUDY

The brains used in this study were prepared by injecting Müller's solution through the internal carotid and vertebral arteries. They were then placed in the solution for a period of six weeks. Müller's solution was not injected into the spinal cord, but after opening the dura mater the cord was immersed in the solution for six weeks. At the end of this time the brain was sectioned, and representative blocks were taken from the spinal cord and brain stem. The thalamus was cut serially in slabs 2 mm. thick. These were then immersed in a solution containing 1 part of a 1 per cent aqueous solution of osmic acid to 2 parts of Müller's solution. This solution was changed every week or ten days. At the end of three weeks the blocks were examined and a small nick made in the side to make certain the block was thoroughly infiltrated with osmic acid. (The block should be uniformly dark brown; the presence of a central yellow layer is indicative of incomplete infiltration.) If the blocks were uniformly brown they were washed for twenty-four hours in running water and then rapidly dehydrated. Rapid embedding was accomplished by placing the blocks in a 6 per cent solution of pyroxylin in alcohol and ether in a tightly covered jar and kept in an incubator at a temperature of 56 C. for twelve hours (overnight). After the jar was allowed to cool (otherwise gas bubbles form in the pyroxylin), the blocks were transferred to a 12 per cent solution and incubated for from eight to ten hours (during the day). They were then put in a 25 per cent solution of pyroxylin and incubated at 56 C. for twelve hours (overnight). The embedding took about thirty-six hours and the infiltration of the pyroxylin was equal to that seen after several weeks of embedding at room temperature. The individual blocks were then placed in small paper cups and covered with a 25 per cent solution of pyroxylin. The cups were immersed in chloroform, where they hardened within a few hours. Sections from these blocks were cut at 40 microns, as with ordinary pyroxylin material. They were easily handled and rarely cracked. This rapid method of embedding is far superior to the old rapid method, in which the sections are brittle, crack frequently and can be handled only with great difficulty, and in which the final result is inferior to those obtained by the present method.

REPORT OF CASES

CASE 1.—*History.*—G. H., a salesman aged 48, was referred to the neurosurgical service because of severe pain in the right side of the chest for the previous year. Three years prior to admission he had consulted a physician because of a cough and loss of appetite for three months. Medicinal therapy improved his condition, but when the symptoms recurred three months later a roentgenogram of the chest revealed tuberculosis of the right lung with cavitation. The sputum contained tubercle bacilli at that time. About one year before admission pneumothorax was started, but because good collapse could not be obtained pneumolysis was performed on May 4, 1937. After this procedure the patient experienced a pulling pain along the right side of the chest, which was aggravated by deep breathing and sometimes by swallowing. Hypnotics gave no relief. The pain gradually increased in severity until sleep became difficult. On Jan. 28, 1938,

right phrenicotomy was performed, but was apparently incomplete, for there was little change in the movement of the diaphragm. The pain persisted. On May 21, 1938, the fifth to the eleventh intercostal nerves were sectioned, without relieving the pain.

Examination.—At the time of admission to the University of Chicago Clinics, on June 12, 1938, the patient showed clinical and roentgenologic evidence of pneumothorax on the right side. A long scar was present along the lower thoracic portion of the spine on the same side. There were complete anesthesia on the right side of the chest between the fifth and the tenth dorsal segment and a reversed Beevor sign, the umbilicus being drawn down and to the left when the head was elevated. Palpation confirmed the paresis of the right upper abdominal muscles.

Course.—On June 16, 1938, 120 mg. of procaine hydrochloride in 5 cc. of cerebrospinal fluid was injected into the lumbar subarachnoid space and good anesthesia obtained to the level of the third dorsal segment. The pain was slightly diminished during the period of anesthesia. On June 18, 1938, right phrenic exeresis was performed, without influencing the pain. On June 27, 1938, left anterolateral chordotomy between the eighth cervical and the first thoracic root was performed by Dr. Paul C. Bucy, with the patient under ether anesthesia. After this procedure there was complete analgesia below the fifth dorsal dermatome, with preservation of touch and proprioceptive sense below the tenth dorsal dermatome. The patient had an uneventful convalescence, but complained off and on of the former pain. On July 16, 1938, eighteen days after chordotomy, he committed suicide by jumping four stories from his window.

Autopsy.—Examination of the body, carried out three hours post mortem, showed: multiple fractures of the jaw, left clavicle, right shoulder, left tibia and ribs; chronic pulmonary tuberculosis of the upper and middle lobes of the right lung and the upper lobe of the left lung; traumatic rupture of the liver, right renal artery and right lung, and a freshly healed incision in the spinal cord.

Examination of the Central Nervous System.—Gross Examination: No abnormality was apparent on examination of the spinal cord and brain except a small lesion just anterior to the dentate ligament, 3 mm. in length, on the left side of the spinal cord, just above the first thoracic root. The spinal cord was immersed in Müller's fluid. Müller's solution was injected into the brain, and it was placed in this solution. After hardening, sections for the Marchi technic were taken from the spinal cord at the following levels: the second, fifth, seventh and eighth cervical and the third, seventh, tenth and twelfth dorsal. The block containing the lesion at the eighth dorsal segment was embedded and cut serially, and every other section stained for myelin. Four representative blocks were taken from the brain stem for the Marchi technic. After treatment by the Marchi technic, the thalami were sectioned serially at 40 microns, and every second section was mounted.

Microscopic Examination: 1. Lesion: Serial sections through the lesion stained for myelin showed a triangular cut placed just below the dentate ligament, extending to the lateral angle of the anterior horn and reaching inferiorly the surface just lateral to the exit of the anterior roots. It had not damaged the anterior column and had just reached the anterior horn.

2. Spinal cord: Below the lesion there was no significant degeneration. In the cervical portion of the cord above the lesion considerable pseudo-Marchi degenera-

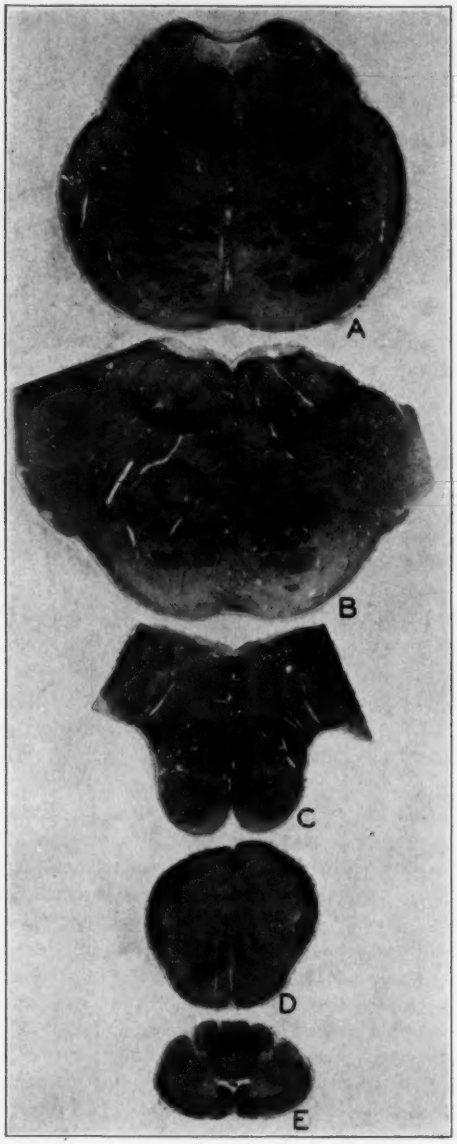

Fig. 1 (case 1).—Photomicrographs of sections of the brain stem, with the site of the degenerated fibers of the spinothalamic tract indicated by black dots. *A*, is through the upper part of the pons; *B*, through the lower part of the pons; *C*, through the medulla oblongata, at the level of the olive; *D*, through the lower part of the medulla oblongata, and *E*, through the second cervical segment.

tion was scattered over the entire section, but there appeared to be more of the dust in the left anterolateral sector of the cord.

3. Brain stem: The sections of the brain stem were of much better quality than those of the spinal cord, and the degeneration was clearly recognizable. At the level of the first cervical segment, just below the substantia gelatinosa Rolandi (the nucleus of the descending root of the fifth nerve), was a triangular area of scattered Marchi degeneration, the base of which lay against the periphery of the spinal cord. This area outlined the descending root of the fifth cranial nerve. With the appearance of the inferior olivary nucleus this degeneration came to lie on the periphery of the spinal cord between the inferior olivary nucleus and the restiform body. The fibers of the descending root of the fifth cranial nerve lay dorsal to it.

In the middle of the pons the degeneration of the spinothalamic tract lay just medial to the middle cerebellar peduncle and in the extreme lateral portion of the medial lemniscus. In the anterior part of the pons it passed dorsally just lateral to the brachium conjunctivum and just anterior to the middle cerebellar peduncle and lay in the most peripheral portion of the mesencephalon, above the lateral sulcus. A few degenerated fibers of the ventral spinocerebellar tract turned superiorly to reach the upper surface of the brachium conjunctivum (fig. 1).

4. Thalamus: The degenerated fibers were readily traced through the mesencephalon as they passed into the inferior colliculus lateral to the fibers of the posterior longitudinal bundle. On reaching the inferior colliculus a few fibers seemed to pass medially and terminate. The majority of the fibers passed into the inferior colliculus just medial to its brachium and ran dorsally and slightly laterally to reach the inferior margin of the superior colliculus. Some fibers may have ended in the superior colliculus or in the tectum, for there was fine stippling about the tract. As the mesencephalon joined the thalamus, the spinothalamic tract maintained its position medial to the brachium of the inferior colliculus. Further anteriorly, it gradually swung laterally to reach the division between the mesencephalon and the diencephalon. In coronally cut sections it then appeared to be situated in the middle of the bridge between the two. As the brachium of the inferior colliculus passed into the medial geniculate body, the spinothalamic tract broadened and lay along the lower two thirds of the middle of the nucleus limitans, just below the corticotectal tracts. The majority of the fibers then turned laterally just above the medial geniculate body. A few seemed to pass medially along the nucleus limitans and disappear. The remainder of the fibers then rapidly spread out and broke up just above the medial geniculate body in the ventral half of the lateral nuclear mass. They terminated in the extreme posterior part of the nucleus ventralis posterior, the cells of which could be recognized in this preparation by their large size. It is impossible to say how far the ramifications of the terminal branches of the spinothalamic fibers extended. The nucleus centromedianus appeared just rostral to the breaking up of the fibers. There was no evidence that any fibers go to this nucleus or to any of the medially or dorsally lying nuclei (fig. 2).

CASE 2.—*History.*—N. H., a housewife aged 37, was referred to the University of Chicago Clinics by Dr. E. Parsons because of severe pain in the pelvis during the previous year. Seven years previously her uterus had been removed for severe dysmenorrhea. About a year and a half before admission the patient experienced severe perineal pain and vaginal hemorrhage, which was treated medicinally by an outside physician. She continued to have pain and bleeding. In March 1937 she was said to have a carcinoma of the cervix and was given radium and roentgen

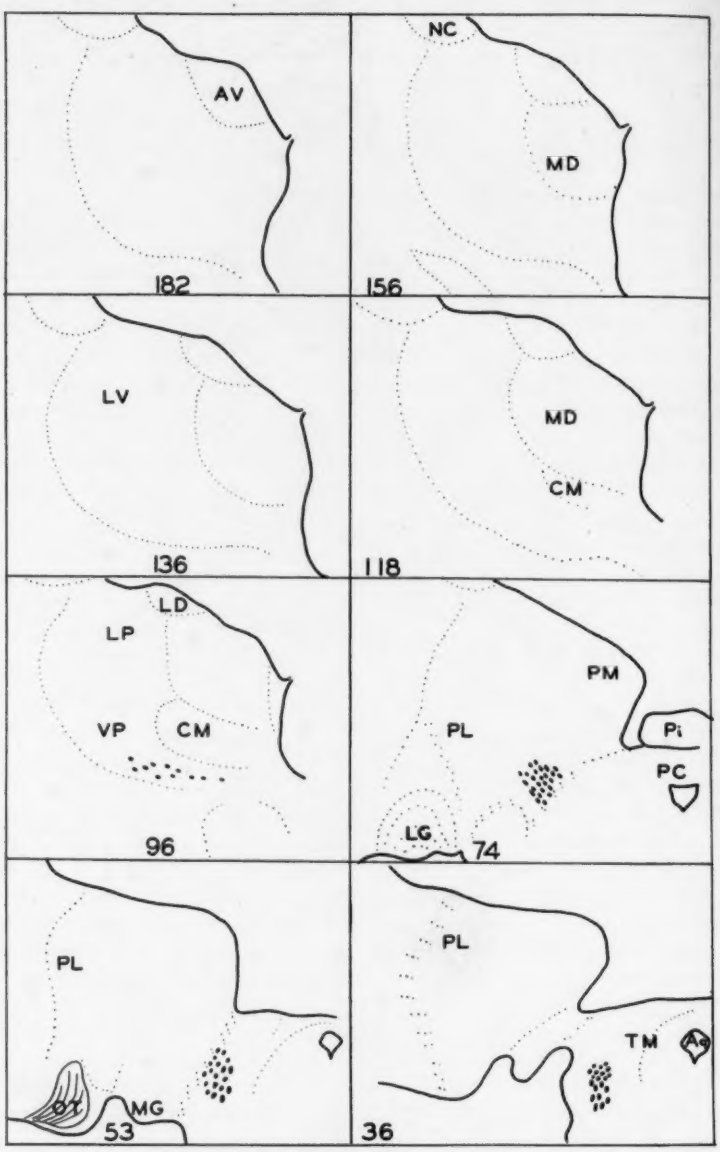

Fig. 2 (case 1).—Semidiagrammatic sketches of serial sections of the left thalamus to show the course and termination of the degenerated spinothalamic fibers (indicated by heavy black dots).

The following abbreviations are used in this illustration: *Aq*, aqueductus Sylvii; *AV*, nucleus anteroventralis; *CM*, nucleus centromedianus; *LD*, nucleus lateralis dorsalis; *LG*, corpus geniculatum laterale; *LP*, nucleus lateralis posterior; *LV*, nucleus ventralis lateralis; *MD*, nucleus medialis dorsalis; *MG*, corpus geniculatum mediale; *NC*, nucleus caudatus; OT, tractus opticus; *PC*, commissura posterior; *Pi*, glandula pineale; *PL*, nucleus pulvinaris lateralis; *PM*, nucleus pulvinaris medialis; *TM*, tectum mesencephali, and *VP*, nucleus ventralis posterior.

therapy. The pain persisting, an intraspinal injection of alcohol was carried out three months previous to admission and, no relief being obtained, was repeated a week later. After this procedure she had urinary retention and incontinence of the bowels, with motor and sensory paralysis of the left leg. The urinary retention disappeared after a few weeks, but the monoplegia and pain persisted. The latter was not relieved by analgesics or sedatives, other than morphine, and prevented sleep.

The remainder of her history was essentially without significance, except for loss of 40 pounds (18.1 Kg.) in weight in the previous year.

Examination.—At the time of admission, on Sept. 19, 1937, the patient was emaciated, but showed no physical abnormalities other than those related to the genital and nervous systems. The vagina was constricted and tender. The vault bled when touched. Pelvic examination revealed a tender, fixed mass extending to the brim of the pelvis.

The patient was well oriented and alert. No abnormalities were noted in the cranial nerves. There were marked weakness of all movements of the left lower extremity and slight weakness of the right leg. Appreciation of pinprick, cotton and temperature was impaired over the left leg to the hip, markedly so below the knee. There was definite hyperesthesia below the right knee. An area of hypesthesia to pinprick, cotton and temperature was present in the right saddle region. Position and vibratory senses were impaired in the left leg.

Operation.—On September 21, with local anesthesia, supplemented by ethylene at the time of section, bilateral chordotomy was performed between the third and the fourth thoracic vertebra. Complete analgesia resulted below the sixth thoracic dermatome. The pain was completely relieved. The patient was unable to void and required catheterization every six to eight hours. Severe cystitis developed, but subsided within a few days. On September 28 she was discharged.

Course.—The patient had no further pain, but cystitis persisted in spite of all treatment. She became weaker and died of uremia on December 16, twelve weeks after chordotomy.

Autopsy.—Examination of the body, carried out approximately eight hours after death, revealed local pelvic carcinomatous invasion, but no evidence of metastases to the liver, spleen, lungs or spinal cord. There was severe cystitis, with bilateral pyonephrosis. Müller's solution was injected into the brain. The brain and the spinal cord were immersed in Müller's solution.

Examination of the Central Nervous System.—Gross Examination: The spinal cord and brain showed no abnormalities. Only small anterolateral scars on the cord indicated the site of operation.

Representative sections were taken from the spinal cord for the Marchi technic. The block containing the lesion was embedded and sectioned serially, and every other section stained for myelin. Representative blocks were taken from the brain stem for Marchi staining. The thalami were cut coronally in blocks from 1 to 1.5 mm. thick, and a representative section was taken from each block after treating with the Marchi technic.

Microscopic Examination: 1. Site of the lesion: The incision had been made on both sides anterior to the level of the base of the posterior columns. It had extended into the substance of the anterior horns and then passed externally, not damaging the anterior column on one side and cutting through the cap of the column on the other side. On the left side the substance of the anterior horn was damaged to some extent, but on the opposite side the anterior horn was free from injury.

2. The spinal cord: Marchi sections just below the lesion showed scattering of Marchi globules in the anterolateral columns on both sides. These globules were particularly pronounced in the lower portion of the pyramidal tracts. A section from the eleventh dorsal segment showed Marchi globules in the anterolateral tracts and in the lower part of the pyramidal tract, particularly. Above the lesion the Marchi degeneration was much more pronounced, and on the left side extended to the periphery in the region of the spinocerebellar tracts. At the level of the first cervical segment and of the nucleus gracilis, just below the nucleus of the descending root of the fifth nerve was a zone of scattered Marchi degeneration, somewhat more extensive on the left side than on the right.

3. Brain stem: At the level of the middle of the inferior olive the degeneration was less pronounced and was situated peripherally, just above the lateral margin of the fibers surrounding the inferior olive. The degenerated fibers were rather scattered. The degeneration maintained this position in the upper part of the bulb. In the pons it was seen scattered over the dorsal surface of the lateral lemniscus as the latter passed above and lateral to the brachium conjunctivum.

4. Thalamus: The spinothalamic tract, which was recognized by scattered degeneration, was seen passing medial to the brachium of the inferior colliculus. It then passed dorsally to the junction between the thalamus and the mesencephalon, and turned abruptly laterad. After turning laterally into the thalamus at this level, posterior to the beginning of the nucleus centromedianus, the degeneration dispersed and could not be traced further.

COMMENT

The clinical findings in these cases following section of the spinothalamic tracts are typical. The relief of pain, partial in the first case and complete in the second, analgesia and thermoanesthesia, with relatively little involvement of tactile sensibility, below the level of the lesion are characteristic of anterolateral chordotomies. Although pain and temperature sensibilities are chiefly involved by such procedures, touch sense is not entirely spared. The number of touch points per cubic centimeter is reduced; the threshold of the individual point is heightened, and the chronaxia is lengthened. In cases of unilateral chordotomy these disturbances are present on both sides of the body, indicating the bilateral origin of the fibers of the anterolateral column of the spinal cord. The upper level of these disturbances in tactile sensibility is one or two segments below the level for pain and temperature. This is explained by assuming that the fibers mediating touch do not cross immediately, but run up several segments of the spinal cord before passing across to the opposite anterolateral column.

The anatomic observations are similar to those of previous investigators, who studied more complete transections of the spinal cord. Because only the anterolateral tracts are involved in these cases, the degeneration is much less extensive. It is evident that the number of degenerated fibers which reach the thalamus is much less than the number of degenerated fibers in the spinal cord just above the lesion. This disparity is

the result of the termination of many fibers in the bulb, pons and tectum. It has been suggested that this arrangement may serve complicated reflexes and/or act as short relays to the thalamus. It may, therefore, be one mechanism responsible for the restitution of pain sensibility after anterolateral chordotomy.

The termination of the spinothalamic tracts in the basal and ventral part of the thalamus is similar to the endings of this system in other primates. In the monkey, after complete transection of the spinal cord, considerable degeneration can be traced to the nucleus ventralis posterior of the thalamus. After a hemisection the degeneration is much less. In the chimpanzee, the number of degenerated fibers which reach the thalamus are indeed few—in fact, about as many as reach the thalamus in man. This suggests that short relays to the thalamus play a more prominent role in conduction of pain and temperature sensibilities to the thalamus in the higher primates and man than in the lower members of this group.

The paucity of degeneration within the thalamus precludes a statement about the exact distribution of the terminal fibers of the spinothalamic tract in the posterior and ventral parts of the thalamus. In correlation with the termination of the medial lemniscal tracts within the posterior ventral nucleus of the thalamus, Le Gros Clark [6] and I [7b] have suggested that the fibers of the spinothalamic tract may have a mediolateral arrangement within the thalamus, those originating from the more rostral parts of the body terminating medially and those from the caudal parts ending laterally. The present study can offer no direct evidence on this point.

THE ORIGIN, COURSE AND TERMINATION OF THE SPINOTHALAMIC TRACT

The correlation of clinical and histologic studies in cases of anterolateral chordotomy has given considerable information concerning the finer arrangements of the spinothalamic tracts.

Origin of the Spinothalamic Tracts.—The earlier investigators concluded that the spinothalamic tract arises from the cells lying within the posterior horn just ventral to the substantia gelatinosa. In fact, the name nucleus centrodorsalis spinothalamicus was assigned to this group of cells. Foerster and Gagel [11] studied the retrograde cell changes in the spinal cord following anterolateral chordotomy. They were able to detect changes in the large cells about the posterior horn; all other cells of the spinal cord, including those of the substantia gelatinosa, were normal. Foerster and Gagel [11] divided these large cells into three groups: a basal, a pericornual and an apical group (fig. 3), depending on their relationship to the posterior horn. After unilateral chordotomies

the changes are present in the large cells around the posterior horns on both sides, but are more extensive on the contralateral than on the ipsilateral side. Kuru [13] has made a careful analysis of the degeneration found in each of the cellular groups about the posterior horn after anterolateral chordotomy. By comparing the severity of the cellular changes in each spinal segment with the severity of the pain disturbance in the same segment, he has sought to determine more accurately the origin of the spinothalamic tract. By this ingenious method he has shown that the amount of degeneration in the basal group of cells bears no relation to the severity of the disturbances in appreciation of pinprick, but that the severity of the changes in the pericornual and apical groups closely parallels the sensory abnormalities. He therefore concluded that these groups are the cells of origin of the spinothalamic and spinotectal tracts.

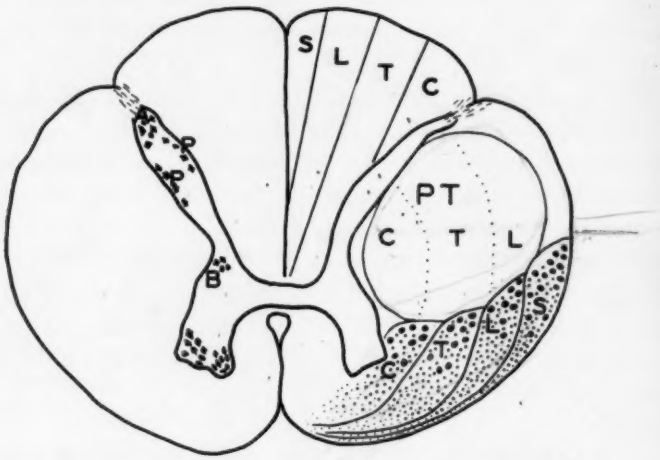

Fig. 3.—Semischematic drawing to show on the left side the cell groups of the posterior horn, and on the right side the arrangement of the spinothalamic and other tracts in the lower cervical region. The heavy dots represent fibers concerned with temperature; the medium-sized dots, fibers mediating pain, and the fine dots, fibers carrying touch and pressure impulses. Note the overlapping and topical arrangement of the fibers.

The following abbreviations are used in this illustration: *A*, apical group of large ganglion cells of the posterior horn; *B*, basal group of large ganglion cells of the posterior horn; *C*, fibers from the cervical segment of the spinal cord; *L*, fibers from the lumbar segment of the spinal cord; *P*, pericornual groups of large ganglion cells of the posterior horn; *PT*, tractus pyramidalis; *S*, fibers from the sacral segment of the spinal cord, and *T*, fibers from the thoracic segment of the spinal cord.

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13. Kuru, M.: Die Veränderung im Zentralnervensystem bei den 2 Fällen von "partieller" Chordotomie: Ein Beitrag zur Frage der Ursprungszellen des Tractus spinotectalis et -thalamicus, Gann **32**:1-25, 1938.

Omitting a discussion of the experimental error in this method, a legitimate criticism might be directed to the criterion taken for the basis of the sensory disturbances. No consideration was allowed for temperature and tactile sensory disturbances. Presumably the author tacitly assumed that these paralleled the impairment of pain sensibility. But such is not always the case. Hence the conclusion that only the pericornual and apical cell groups give rise to spinothalamic fibers must be made with some reservation.

Course in the Spinal Cord.—The fibers arising from the large cells of the posterior horn pass across the midline in the anterior commissure to the opposite anterolateral column. Although it had previously been assumed that this decussation took place over several spinal segments, the experience of Foerster and Gagel [11] with chordotomy has indicated that the crossing occurs within one segment. The fibers immediately after crossing congregate in the anterior columns, but as they ascend in the spinal cord they become more laterally situated. This is due to the fact that the anterior columns containing uncrossed pyramidal fibers become larger in higher segments of the spinal cord, and that more fibers of the spinotectal and spinothalamic tracts are being added at higher segments, displacing laterally those from lower segments. There is thus a topical localization within the spinotectal and spinothalamic tracts, the fibers from the lowest segments lying on the periphery of the cord and those from higher segments more deeply. Superimposed on this rather crude topical orientation is perhaps a rough functional arrangement of the fibers. Foerster and Gagel [11] expressed belief that the fibers mediating temperature sensibility lie in the dorsal part of the anterolateral column and the fibers carrying painful sensations more ventrally, while those relaying pressure and tactile impulses lie in the anterior columns. Such a functional division would have to be a rough one, for clinically one modality is never involved to the exclusion of the others. There may be a varying admixture of the fibers carrying the different categories of sensation, so that dorsally "temperature fibers" predominate, ventrally "touch and pressure fibers" and in the intermediate areas "pain fibers."

One additional feature of the topical arrangement of the fibers of the spinothalamic tract must be emphasized, for it probably explains certain clinical phenomena (fig. 4). As already mentioned, as the fibers enter the anterolateral column they lie anteriorly, but as they ascend in the spinal cord they become displaced laterally and dorsally. Hence the sacral fibers, which lie near the anterior columns in the lumbar region, lie practically lateral to the pyramidal tracts in the cervical portion of

the spinal cord.[14] For this reason, they may be spared in dorsal or cervical anterolateral chordotomies in which the incision is made 1 to 2 mm. anterior to the dentate ligament (fig. 3).

Course in the Brain Stem.—At the caudal border of the bulb the spinothalamic tract lies just anterior to the nucleus and spinal root of the trigeminal nerve. Slightly higher the spinothalamic tract lies on the periphery of the bulb, just dorsolateral to the inferior olivary nucleus. On entering the pons, the spinothalamic tract lies just medial to the

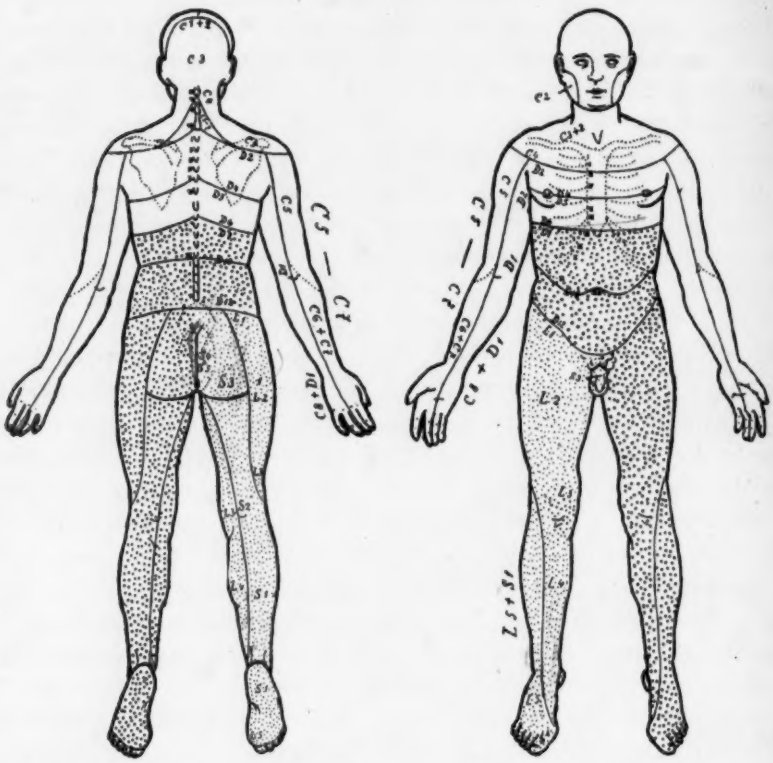

Fig. 4.—Sensory chart to show the areas of hypalgesia (fine stippling) and analgesia (heavy stippling) following anterolateral chordotomy for the relief of pain due to osteoarthritis of the hips. Although the patient had complete relief from pain, he still responded to a 10 Gm. von Frey pin as a painful stimulus on the right leg. A possible explanation of the anatomic basis of this sparing is given in the text.

14. Since writing this manuscript, a paper by Hyndman and Van Epps (Hyndman, O., and Van Epps, C.: Possibility of Differential Section of the Spinothalmic Tract, Arch. Surg. **38**:1036-1053 [June] 1939) has appeared, in which the authors present a similar topical arrangement of the spinothalamic tracts based on anatomicoclinical studies.

middle cerebellar peduncle and lateral to the medial lemniscus. As the ventral spinocerebellar tract turns dorsally, the spinothalamic tract continues rostrally. At the rostral margin of the middle cerebellar peduncle the spinothalamic tract turns dorsally and again comes to lie on the periphery of the brain stem, just superior to the lateral sulcus. The fibers gradually ascend and pass into the caudal part of the inferior colliculus, beneath the point of exit of the fourth cranial nerve.

Although in most lesions of the bulb the entire spinothalamic tract is injured because of its compactness, there is both anatomic and clinical evidence for suggesting a topical arrangement within the tract at this level. The fibers which carry sensory impulses from the caudal parts of the body lie laterally (peripherally) and dorsally; those from the head are more medially and inferiorly situated. As the tract turns dorsad in the mesencephalon, the fibers subserving impulses from the lower extremity are most superiorly placed.

The peripheral position of the spinothalamic tract in the mesencephalon may be utilized in the future for interrupting the pain pathways from the entire opposite half of the body. That complete contralateral hemianalgesia may be obtained from interruption of these fibers at this level is known from clinical and pathologic studies of thrombosis of the superior cerebellar artery [15] and from Dogliotti's [16] surgical section of the tract at this level. In the monkey such a surgical procedure is readily performed.

Thalamus.—After the spinotectal fibers have been given off to the colliculi, the spinothalamic tract passes just medial to the brachium of the inferior colliculus. As the latter enters the medial geniculate body, the fibers of the spinothalamic tract pass above it and just inferior to the corticotectal fibers. Immediately rostrad to these fibers the spinothalamic tract crosses the nucleus limitans along a rather wide base and turns abruptly laterally to disperse in the basal portion of the ventral thalamic nucleus, where the large cells of the nucleus ventralis posterior of the thalamus are evident, even in Marchi preparations. Some fibers of the spinothalamic tract seem to be given off to the gray matter just below the nucleus limitans. None passes into the nuclei centromediani or medialis dorsalis, or the anterior half of the thalamus. In the monkey there appears to be a definite topical arrangement of the termination of the pain-carrying fibers. The fibers from the spinal nucleus of the trigeminal nerve end predominantly in the medial part of the nucleus

15. Russel, C. K.: The Syndrome of the Brachium Conjunctivum and the Tractus Spinothalamicus, Arch. Neurol. & Psychiat. **25**:1003-1010 (May) 1931.

16. Dogliotti, M.: First Surgical Sections, in Man, of the Lemniscus Lateralis (Pain-Temperature Path) at the Brain Stem, for the Treatment of Diffused Rebellious Pain, Anesth. & Analg. **17**:143-145, 1938.

ventralis posterior (usually spoken of as the arcuate nucleus). The fibers from the leg terminate along the external medullary lamina, and those from the arm predominantly in the intermediate area. It must be noted from Marchi preparations that there appears to be considerable overlapping of these terminations. Whether this overlapping is real or apparent, due to the Marchi method, is not known. The dispersion of the fibers of the spinothalamic tract is so abrupt in human preparations that the precise termination within the nucleus ventralis posterior is difficult to determine. Hence, from human material alone no statement can be made regarding the topical ending of the spinothalamic system, but probably the findings in the macaque are also applicable in man.

SUMMARY

The course of the spinothalamic tract is traced from the apical and pericornual cells of the posterior horn across the anterior commissure to the anterolateral columns. It then ascends in this column, its fibers gradually being pushed dorsad, so that just above the pyramidal decussation it lies immediately below the spinal tract of the fifth nerve. In the bulb it lies on the periphery and dorsolateral to the inferior olivary nucleus. Through the pons the spinothalamic tract is just medial to the middle cerebellar peduncle and on the same plane, but lateral to the medial lemniscus. In the mesencephalon it becomes peripheral again, lying just lateral to the brachium conjunctivum. It passes through the colliculi, to which the spinotectal fibers are given off, and then, lying just medial to the brachium of the inferior colliculus, it enters the diencephalon. Turning abruptly laterad, the fibers of the spinothalamic tract terminate in the basal and ventral part of the nucleus ventralis posterior of the thalamus. There appears to be throughout the course of the tract a distinct, although probably somewhat overlapping, topical arrangement.

REMISSIONS IN EPILEPTIC PATIENTS TREATED WITH SODIUM BROMIDE IN AN OUTPATIENT CLINIC

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This paper reports a study to determine the number of cases in which all epileptic attacks are stopped during treatment with sodium bromide. Although in many other cases the number of seizures was diminished, only complete cessation of attacks was considered as adequate clinical response to treatment. When all attacks ceased, a remission was said to have occurred.

All the patients seen at regular intervals in the clinic for epilepsy at the Northwestern University Medical School for a period of six months or more were considered in this report. There were 98 such patients. Of the 98 patients, 47 suffered from grand mal and 50 from both grand and petit mal attacks, and 1 had attacks of petit mal alone. In 69 cases the disease was classified as idiopathic, in 19 as organic and in 10 as focal. By a focal attack is meant that the aura or the attack itself indicated a focal origin, although there were no other objective findings.

In 3 of the 19 cases of organic epilepsy the disease was due to changes resulting from alcoholism; in 4, to cerebral trauma at birth; in 2, to later craniocerebral injury; in 3, to encephalitis; in 3, to vascular accidents; in 2, to tumor of the brain, verified at operation, and in 2, to cerebral syphilis.

Attacks were stopped from the beginning of treatment in 38, or about 38 per cent, of the 98 patients. Three of these patients were treated less than a year. Sixteen had had a remission of six to twelve months; 12, of one to two years; 7, of two to three years; 2, of three to four years, and 1, of eight years. In 9 other cases attacks returned and then a terminal remission occurred. In 6 of these cases the duration

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of remission was from six to twelve months, in 2 from one to two years and 1 from two to three years.

Terminal remissions [1] of at least six months were brought about in a total of 47 of 98 patients, or in approximately 48 per cent.

In 33 additional patients remissions occurred, but were followed by exacerbations. Some of these remissions lasted for months to years. In some cases the exacerbation occurred because the patient discontinued medication without permission. The presence of a single attack constituted an exacerbation.

In 80 patients remissions were brought about as a result of therapy. Eighteen patients were recalcitrant to all forms of therapy in that a remission did not follow, although the number of attacks was diminished.

RELATION OF ETIOLOGIC FACTORS TO REMISSIONS

The percentages of terminal remissions in cases of the idiopathic, focal and organic type were 49, 40 and 45, respectively. Although the figures are not statistically significant, the idiopathic attacks seemed more amenable to treatment.

CHARACTER OF ATTACKS AND REMISSIONS

In 30, or 64 per cent, of the 47 patients with grand mal alone a terminal remission resulted. In 85 per cent a remission was obtained.

In 23, or 46 per cent, of the 50 patients having both grand and petit mal a terminal remission resulted, and in 78 per cent a remission was obtained. In 1 case of petit mal an initial remission occurred.

It can be seen that in cases in which major attacks occurred alone remissions were more readily obtained.

There was no correlation between age of onset of the convulsive state, duration of the disease, number of previous attacks and prognosis.

In 25 of the 98 cases phenobarbital was used in conjunction with sodium bromide. In only 1 of the cases of a terminal remission was phenobarbital of assistance in causing the remission. In the remaining 24 cases the addition of phenobarbital diminished the number of attacks without causing a terminal remission. Of 18 recalcitrant patients, 14 were treated with the two drugs at the same time, without any improvement. It is our belief that in the majority of instances in which sodium bromide is ineffective phenobarbital is also without effect in producing a remission.

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1. The total number of patients with terminal remissions includes those with initial remissions who had no recurrence of attacks and those with terminal remissions whose attacks were finally stopped.

CONCLUSIONS

1. Final remissions beginning with the institution of treatment or shortly after occurred in 47 of 98 cases, or 48 per cent.

2. Remissions were brought about in 80 of 98 cases.

3. In cases of idiopathic epilepsy there was a higher percentage of terminal remissions—49 per cent as compared with 40 and 45 per cent in cases of the focal and the organic type, respectively.

4. In 64 per cent of the patients with grand mal alone a terminal remission occurred, while in 46 per cent with both grand and petit mal a terminal remission was obtained. In patients having only major attacks it is easier to bring about a remission with treatment.

FLACCID HEMIPLEGIA IN MAN

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Permanent flaccidity after cerebral lesions in man is not often described. The condition probably occurs with fair frequency, especially with vascular lesions. Owing to incomplete clinical examination and the lack of examinations subsequent to the initial one, the failure of the limbs to become spastic usually is not recognized. During a period of twenty-two months 10 cases of severe flaccid paresis or paralysis have been encountered in an active neurologic service. The duration of the flaccidity varied from one month to seven and one-half years, to date or until death. In 6 cases the patients died, and in 3 there were postmortem examinations. The pathologic observations did not bear out the clinical impression that the localization of the lesion causing the enduring flaccidity was entirely postrolandic.

There follows a report of the 3 cases in which autopsies were performed.

REPORT OF CASES

CASE 1.—H. W., a white man aged 65, was admitted to the neurologic service of the Cincinnati General Hospital on April 29, 1938. According to a nephew, there had occurred sudden inability to speak on April 17, 1938. He had remained unable to talk, and on April 29 fell out of bed. The physician who attended the patient said that he had had a "stroke." There had been a somewhat similar incident five years before, involving speech and the function of the left extremities. The left extremities had been weak since, but he had regained speech. The nephew was unable to state the handedness of the patient. He did say that "high blood pressure" was common in the patient's family. A brother had died at the age of 53 of a "stroke" and high blood pressure. The patient had been ordered to stop drinking spirituous liquors ten years previously because of high blood pressure.

Examination.—The abnormal findings on admission to the hospital were restless stupor, tortuosity and thickening of the blood vessels of the extremities, a blood pressure of 198 systolic and 88 diastolic, tortuosity of the vessels of the retina, inability to talk even when aroused, moderate atrophy of the muscles of the left extremities and complete and flaccid paralysis of the left extremities and the lower portion of the left side of the face. The tendon reflexes were less active in the left upper extremity than in the right; no reflexes could be obtained from

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the left lower extremity, while those in the right were brisk. Abdominal and cremasteric reflexes were active on the right side and absent on the left. There was no clonus and no response to plantar stimulation.

Course.—The patient gradually became less stuporous, and neurologic examinations, which were necessarily curtailed, were performed at frequent intervals. On May 19, one month after the onset, he was cooperative, and neurologic observations were made. Cranial Nerves: The optic disks were normal; the blood vessels of the retina were extremely tortuous and narrow. There was left homonymous hemianopia in confrontation tests. The patient did not blink when an object approached his eyes from the left and always blinked at those approaching from the right. There was bilateral ptosis. The pupils were 3.5 mm. in diameter. They were equal in size and regular in outline, and reacted promptly and through a good range to a flashlight. He had not been able to move his eyes to the left beyond the midline since the first examination. The corneal reflexes were normal. There was complete paralysis of the lower portion of the left side of the face.

Motor System: Aphasia was severe. The patient was never heard to utter a word (during four months of observation), although apparently he made great effort to speak. There were no close relatives, and no one could state which hand was the dominant one. He held a pencil correctly with the right hand and made ineffectual attempts at writing. He occasionally seemed to write a few words, all of which were illegible. He repeatedly tried to converse and appeared annoyed at his inability to do so. He pointed with his right fingers and made all sorts of motions and signs with them, none of which were understood. When attempting to speak he continually snapped the fingers of his right hand and wrinkled his brow. When the bed became soiled he would rap on the bed with his right fist until it was changed. On request he pointed with his right hand to parts of his anatomy. There was left hemiplegia, which remained profound until his death. Both the left shoulder and the hip girdle were included in the complete paralysis. Measurement of the extremities did not reveal any great difference in the circumference of the left limbs as compared with the right. Resistance of the left extremities to passive manipulation was markedly reduced, so much so that the left extremities were at all times considered to be flaccid by the examiners.

Sensation: Sensory examination could not be performed because of the aphasia. At all times the patient appeared to appreciate pinprick equally on the two sides of the face and in the right and left extremities.

Reflexes: The reflexes of the upper extremities were brisk, except for the left radial periosteal reflex, which was reduced in amplitude. The tendon reflexes of the right lower extremity were brisk; those of the left were not obtained, although a crossed adductor response resulted on tapping the quadriceps femoris tendon on either side, that on the left being the more active. Hamstring jerks were present bilaterally and were obtained with minimal stimuli. The abdominal and cremasteric reflexes were absent. There was no Hoffmann response and no clonus. The left great toe was in a continual position of dorsiflexion; Babinski, Chaddock and Oppenheim responses were obtained on the left, but not on the right. There was a Gordon reflex on the right.

There was no important change in the neurologic findings up to the time of his death. Occasionally the abdominal reflexes could be elicited on the right, but never on the left. Repeated measurements were made of the circumference of the limbs, for there appeared to be atrophy of the flabby musculature of the left extremities. There was not much difference in the circumference of comparable

parts of the extremities of the two sides. The paralysis and flaccidity remained complete. Lobular pneumonia developed, and the patient died on Aug. 8, 1938, four months after the final ictus.

Autopsy.—This was performed ten hours after death. Abnormalities other than those in the central nervous system were: purulent bronchitis, lobular pneumonia, pulmonary congestion and edema and generalized vascular sclerosis.

The brain was sectioned after it had been fixed for two months in dilute solution of formaldehyde U. S. P. (1:10). The vessels of the circle of Willis were thickened and contained numerous plaques of calcification. The middle cerebral artery on the right contained an organized thrombus, 4.5 cm. distal to the point of origin of the artery from the circle of Willis. On the surface of the right cerebral hemisphere was a large area of softening which involved the superior half of the first temporal convolution, extending posteriorly to the angular gyrus (area 22), most of the parietal association areas (areas 5 beta and 7 alpha) and the entire occipital association area (area 19). These were localized numerically according to Foerster's cytoarchitectural map of the human brain (Fulton[1]).

Coronal sections of the cerebrum, 1.5 cm. thick (fig. 1), revealed that the softening involved the following structures on the right: the superior temporal convolution, the posterior one sixth of the caudate nucleus, the posterior half of the lenticular nucleus and the posterior half of the claustrum and external capsule. The softening cut directly across the posterior half of the internal capsule. Posteriorly, the entire inferior parietal gyrus was softened, as was the superior portion of the inferior temporal gyrus.

The softening was obviously an old one. Where it had involved the basal ganglia it was cystic; the walls of the cavity were lined by a tough, granular, yellow-brown tissue, and fine strands of the same material divided the cyst into numerous cavities. The softening posterior to this area was not cystic, but the cerebral tissue had degenerated into a granular, cheesy mass.

There was another softening, of greater age, in the left hemisphere, involving the superior half of the inferior frontal gyrus (fig. 1).

Microscopic examination (cell studies) of the softening in the right motor area (area 4) and stains of the brain stem for myelin sheaths and fat did not add to information obtained by gross examination. There were obvious loss of myelin sheaths and a moderate amount of the simpler fats in phagocytic cells (scarlet red stain) in the right pyramidal tract of the brain stem. The softening in the left inferior frontal gyrus had reached the stage at which phagocytes were no longer present, and the nerve tissue had been replaced by numerous capillaries and gliosis. The extensive lesion in the right hemisphere was undergoing phagocytosis. Hematoxylin and Van Gieson stains of the thrombus demonstrated microscopically the completeness of the occlusion.

CASE 2.—A. B., a Negro aged 48, was admitted to the neurologic service of the Cincinnati General Hospital on Aug. 17, 1938. No detailed history of his illness was obtained, as he had no relatives and his speech defect rendered him mute for all practical purposes. He had been brought into the hospital by the police, who had picked him up because they thought him to be suffering from heat exhaustion. A friend with whom he boarded said that he had been well, except for an occasional headache, until August 10. On August 11 he had been sent home from his job as an outdoor laborer because he could not see well.

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1. Fulton, J. F.: Spasticity and the Frontal Lobes, New England J. Med. **217**:1017-1024, 1937.

The visual difficulty persisted, and on August 13 he was rendered speechless. On the following day he could not use his right limbs and was incontinent of urine and feces. He would not respond to questions, although he seemed to recognize people. Handedness was not inquired about.

Examination.—The blood pressure was 158 systolic and 104 diastolic. The vessels of the retina were tortuous and narrow. Confrontation tests revealed

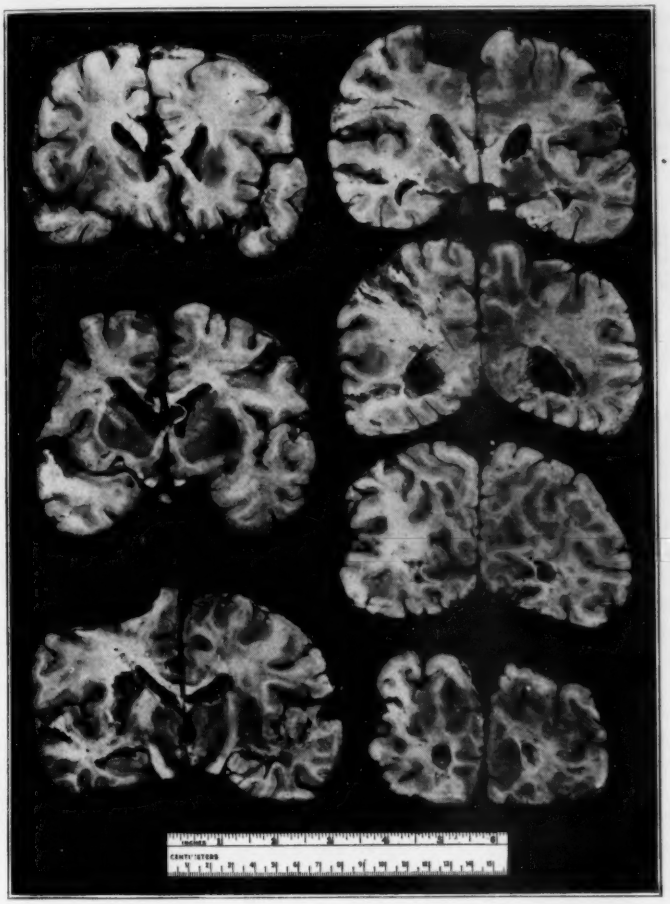

Fig. 1 (case 1).—Coronal sections, 1.5 cm. in thickness, of the cerebral hemispheres, to show the extent of softening in the right hemisphere. (The right motor area, which had been removed for cell study, was normal.)

right homonymous hemianopia. The pupils, which were 3 mm. in diameter, reacted through a small range to a flashlight. Corneal reflexes were present on both sides. There were paralysis of the lower part of the right side of the face and complete flaccid paralysis of the right extremities. The patient was unable to speak. He responded only slightly to pinprick in the right extremities, and promptly to this stimulus in the left extremities. The reflexes in the upper

extremities were equal on the two sides. The achilles tendon reflex was not obtained; the knee jerk was reduced in volume on both sides, but was more active on the left than on the right. The abdominal and cremasteric reflexes were active on the left and absent on the right. No Hoffmann response or clonus was obtained. Plantar responses were extensor in type on the right and flexor on the left.

Course.—On repeated examinations, the neurologic condition remained practically unchanged. Neurologic examination on Oct. 24, 1938, during which the patient was cooperative, revealed the following: Cranial Nerves: There was right homonymous hemianopia in confrontation tests. Movements of the eyes were full in all directions. Movements of the jaw were normal. Corneal reflexes were present. Complete paralysis of the lower portion of the right side of the face was observed. The patient was unable to keep the eyelid down against resistance on the right, but could do so on the left. The brow was wrinkled equally on the two sides. The head was rotated fully to either side, and the tongue protruded in the midline.

Motor System: Handedness was not known. Aphasia of the receptive-expressive type was present. The patient was unable to write with his left hand; he held the pencil fairly well and made illegible or unintelligible marks. He obeyed simple requests, but perseverated. He was probably unable to read, for when printing or writing was presented upside down to him he stared at it, but did not correct its position. He used a cup and a towel correctly with his left hand. He put on his socks with his left hand and demonstrated the use of a percussion hammer by swinging it against his knee. He was unable to demonstrate the use of a match, despite urging. The only words he spoke spontaneously were "yes, sir" and "no," and he did not use them correctly. Pinprick or plantar stimulation called forth a flurry of jargon, and he would laugh and shake his head from side to side in a "no" gesture. As a rule he was happy. He laughed loud, long and frequently. Not the slightest voluntary movement was present in the right extremities, including the girdles. The right shoulder girdle drooped markedly when the patient was in the sitting position. The right extremities were completely flaccid. Circumferential measurement of the extremities gave the following results: The right arm 20 cm. above the olecranon was 22.5 cm., the left, 26.8 cm.; the right forearm 15 cm. below the olecranon was 20.5 cm., the left, 22.9 cm.; the right thigh 10 cm.. above the superior border of the patella was 32.6 cm., the left, 33.2 cm.; the right leg 15 cm. below the inferior border of the patella was 30 cm., the left, 31.3 cm. The right hand and foot were edematous, but there was no edema of the forearm or leg. In the face of generalized muscular atrophy and edema of the right extremities, the circumference of the right hand was 20.9 cm.; that of the left, 20.6 cm.

Sensation: It was impossible to test for sensation. The patient was able to appreciate pinprick better in the right extremities than he had been for a week after his admission. He winced to pinprick on both sides of the face and trunk and on any of the extremities.

Reflexes: The tendon reflexes were much more active in the right limbs than in the left. Tests for the right radial periosteal reflex resulted in contraction of the biceps muscle and some flexion of the fingers and thumb. The left abdominal reflexes were more active than the right. The Hoffmann, Chaddock and Babinski signs were present on the right. There was no clonus. The left plantar response was flexor in type. Reflex flexor withdrawal occurred on plantar stimulation of the right foot.

There were severe scaling of the skin of the palm of the right hand and some edema of this member.

The right fingers gradually assumed a slightly flexed position (at the metacarpophalangeal joints). These fingers could be passively extended without difficulty. The patient would never passively move his paralyzed limbs with his normal left hand, and they remained in the same position practically all the time. If any one moved them he grimaced in pain and made grunting noises. The skin of the right palm desquamated, and a peculiar obnoxious odor emanated from this hand.

The last thorough neurologic examination was performed two weeks before his death. The flaccidity and paralysis of the right limbs and the aphasia were profound and unchanged. Pinprick was more obnoxious over the left extremities than the right. The tendon reflexes were more active on the right, and the plantar response was extensor on that side.

The patient had been able to sit about the ward since his admission. On the day of his death, Jan. 14, 1939 (five months after the onset), he had been sitting in a chair during the morning. Shortly after being put to bed he became cyanotic; respirations were gasping, and there was profuse perspiration; he died within ten minutes after these signs appeared.

Autopsy.—This was performed six hours after death; the observations other than those on the nervous system were: moderately advanced, generalized arteriosclerosis; hypertrophy and slight fibrosis of the myocardium; chronic passive congestion of the viscera, and pulmonary edema.

The brain was placed in dilute solution of formaldehyde U. S. P. (1:10) and was examined after fixation for ten days. On the surface of the left cerebral hemisphere was a large area of softening which involved the first and second and the superior portion of the third temporal convolution (areas 20, 21 and 22) and the occipital association area (area 19). The entire left cerebral hemisphere was reduced in size (fig. 2).

The vessels of the circle of Willis were moderately thickened, and occasional hard, yellow plaques were scattered through them. At a point 1.5 cm. from the origin of the left middle cerebral artery from the circle of Willis was a large thrombus, which measured 2 cm. in its longitudinal extent. The vessel was dissected away from the brain, pinned down and opened longitudinally. The thrombus was completely organized and white in the proximal 1 cm. of its extent. The distal portion contained stratified, brown-gray tissue, evidently built layer on layer from the endothelium inward.

Coronal sections of the cerebrum, 1 to 1.5 cm. in thickness (fig. 2), and of the brain stem, 5 mm. in thickness, were made. The structures supplied by the left middle cerebral artery were involved in an old softening, which extended from within 4 cm. of the tip of the frontal pole backward throughout the left hemisphere, involving the inferior occipital gyrus of the occipital lobe. Specifically included in the softening were the entire temporal lobe, except the uncinate area; the white and gray matter of the island of Reil; the inferior and lateral portions of the middle frontal gyrus; the superior half of the inferior frontal gyrus; the superior and inferior parietal gyri, and the inferior occipital gyrus. Also destroyed were the superolateral third of the caudate nucleus and practically all the putamen; the remaining portions of the basal ganglia were greatly reduced in size. The external capsule was destroyed and the internal capsule completely severed by the lesion. The optic radiation was interrupted in the occipital lobe. The left lateral ventricle was dilated moderately throughout its extent.

The softening was irregularly cystic, and in its greatest extent consisted of white, amorphous material.

All sections of the brain stem were stained by the Loyez method for myelin sheaths; apparently, complete degeneration of the myelin sheaths of the left pyramidal tract had occurred.

Cross sections of the thrombus in the middle cerebral artery were stained by the hematoxylin and eosin and hematoxylin and Van Gieson methods. These sections proved that the thrombosis was complete.

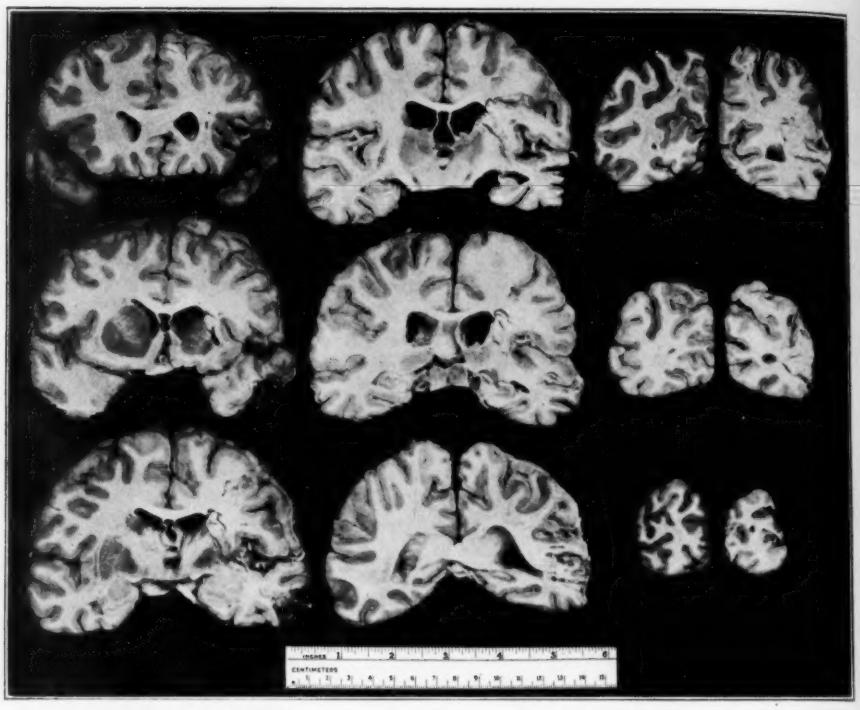

Fig. 2 (case 2).—Coronal sections, 1.5 cm. in thickness, of the cerebral hemispheres, to show the extent of softening in the left hemisphere.

Case 3 (case 6 in table).—J. H., a white man aged 67, was admitted to the neurologic service of the Cincinnati General Hospital on Oct. 6, 1938. He had suffered a sudden onset of left hemiplegia on the evening before his admission to the hospital. The onset was accompanied by some confusion and a state of semiconsciousness. Abnormal findings in systems other than the nervous system were moderate thickening and tortuosity of the arteries of the extremities and a blood pressure of 210 systolic and 70 diastolic. The blood pressure returned to normal (140 systolic and 70 diastolic) after the second day in the hospital and remained normal thereafter.

Neurologic Examination.—Examinations were made repeatedly during the seven and a half months of his stay in the hospital. The findings on October 24 are

recorded here. The patient was cooperative and intelligent. There were occasional periods of confusion during the examination.

Cranial Nerves: The optic disks were normal. The blood vessels of the retina were tortuous, and the arteries presented an increased light reflex. There was arteriovenous compression at the points where the vessels crossed in the retina. The visual fields appeared normal in confrontation tests. The movements of the eyes were normal. The pupils were 3 mm. in diameter. They reacted promptly and through a fair range to a flashlight.

On admission to the hospital there had been slight loss of all forms of sensation in the left side of the face and forehead. At this examination no defect in facial sensation could be demonstrated. There was marked weakness of the lower part of the left side of the face; only the slightest movement was present when the patient attempted to show his teeth or puff out his cheeks. He was unable to keep the left eyelid closed against resistance. The forehead moved well on both sides. The rest of the examination of the cranial nerves gave normal results.

Motor System: The patient used his right hand for writing. There were no signs of aphasia. There was complete paralysis of the left extremities, including the shoulder and hip girdles. The left shoulder girdle drooped markedly when he was in a sitting position. The resistance of the left extremities to passive movements was markedly reduced. There was no muscle atrophy. The right extremities were normal.

Sensory Examination: There was the slightest loss of appreciation of pain, temperature and touch in the left extremities as compared with that in the right. The patient said spontaneously that there was no sensation of "tickle" in the left extremities. However, with his eyes closed he did not miss touch stimulation with a few wisps of cotton of the left extremities. He appreciated small passive changes in the position of his left toes, but passive movements had to be of greater excursion in the left fingers before he could recognize them. He was unable to find his left hand when his eyes were closed. He would grope about, usually find the examiner's forearm and follow it distally until he reached his own forearm and hand. Usually he was able to identify the shape of objects which were placed in his left hand when his eyes were closed. The following stereognostic tests were made: A comb placed in his left hand elicited the response that "the shape is there, but there are no teeth." Nevertheless, he named the object as a comb. When the comb was transferred to his right hand, he stated: "Now I feel the teeth." A rough, round metal rod, 10 cm. in length and 3 mm. in diameter, was described as follows: "It is rough, has four corners and is of small circumference. I think it is a pencil." When it was transferred to his right hand, he immediately said: "There are no corners on it." A flat piece of wood with smooth surfaces he identified as a comb with his left hand, but stated that he could not feel the teeth. When it was transferred to his right hand he described it correctly. Many other objects were tested in this manner, and while he described them fairly well when they were in his left hand, he could usually identify them only when they were transferred to his right hand. He was unable to localize touch sensation in the left extremities. He usually missed the points stimulated by as much as 6 cm. When the left hand or fingers were touched he referred the stimulus proximally, whereas if the forearm or arm was stimulated he referred it distally. Figure writing on the skin was affected in the left extremities; he missed about one third of the tests, and there was always a considerable lag between the stimulus and his response, whereas this lag was

not present on testing figure writing in the right extremities. He recognized two points on the right extremities; on the left he was unable to do so.

Reflexes: The biceps and triceps reflexes were equal on the two sides. The right radial periosteal reflex was more active than the left. The tendon reflexes of the lower extremities were all obtained with minimal stimuli; they were extremely active. There were seven or eight beats of ankle clonus on the left and none on the right. Slight flexion of the left thumb was obtained in tests for the Hoffmann response. The left abdominal reflexes were not obtained; those on the right were active. The plantar responses on the right were all flexor in type. Tests for the Babinski or Chaddock response on the left resulted in quick dorsiflexion of the great toe, with flexor withdrawal of the entire left lower extremity. There was no fanning of the toes, but if the stimulus was severe all of the toes joined in the dorsiflexion. Oppenheim and Gordon tests gave negative results on the left.

The skin of the palm of the left hand was desquamating, while that of the right was not. The temperature of the extremities was normal on palpation.

Course.—There was practically no change in the neurologic condition during the remainder of the patient's life. He presented occasional periods of confusion. In early November pitting edema developed in the left foot and ankle, and the left extremities exhibited a striking degree of cyanosis. Return of voluntary movement in the left lower extremity was observed first early in December, when he was able to make slight movements of flexion and extension of the leg on the thigh. No movement whatever was possible with the toes or about the left ankle or hip. On Dec. 11, 1938, it was thought that the resistance to passive movement of the left lower extremity was normal, but because of the slight return of strength about the knee, the patient tended to hold the left extremities against passive manipulation. In support of the belief that resistance to passive manipulation was reduced was the fact that with the patient in the sitting position the left knee jerk was pendular. The skin of the palm of the left hand had become very soft, and had the feel of velvet. The pads of the fingers were extremely soft. The skin of the left hand was red. At this examination there was some edema of the left hand and foot. It was impossible completely to flex the fingers of the left hand passively because of contracture, although they could be extended completely. The girdles on the left side remained conspicuously paralyzed. The facial paralysis also was unchanged. The results of sensory examination remained unchanged. There was striking inability to locate either of the left extremities in space, although he groped in the proper direction when the left upper extremity was moved. The tendon reflexes were active. The abdominal reflexes were weak and were exhausted after two or three trials. The plantar responses on the left side were extensor in type.

Atrophy of the small muscles of the left hand became evident, and an active Hoffmann response was obtainable from the left hand in March 1939. In early May cellulitis developed in the right foot. On May 11 there were signs of bronchopneumonia, and the patient died on May 18. The flaccid paralysis had remained practically unchanged since the onset, during an observation period of seven and a half months.

Autopsy.—This was performed thirty hours after death, but the body had been embalmed immediately post mortem. The following abnormalities other than those of the nervous system were observed: extensive superficial ulceration of the right ankle, with cellulitis; acute bronchitis and lobular pneumonia; pulmonary edema and congestion; aortic atherosclerosis and cardiac dilatation.

The brain was placed in a dilute solution of formaldehyde U. S. P. (1:10) and was examined after fixation for ten days. The first and second temporal convolutions on the right were softer than those on the left; scattered along the convolutions were small, yellowish brown depressions, which were shallow. The process on the surface appeared to involve the inferior portion of the sensory strip and a portion of the parietal association areas (areas 1, 2, 3 and 7 beta).

The vessels of the circle of Willis were normal in distribution; they were slightly thickened, and there was no formation of plaques.

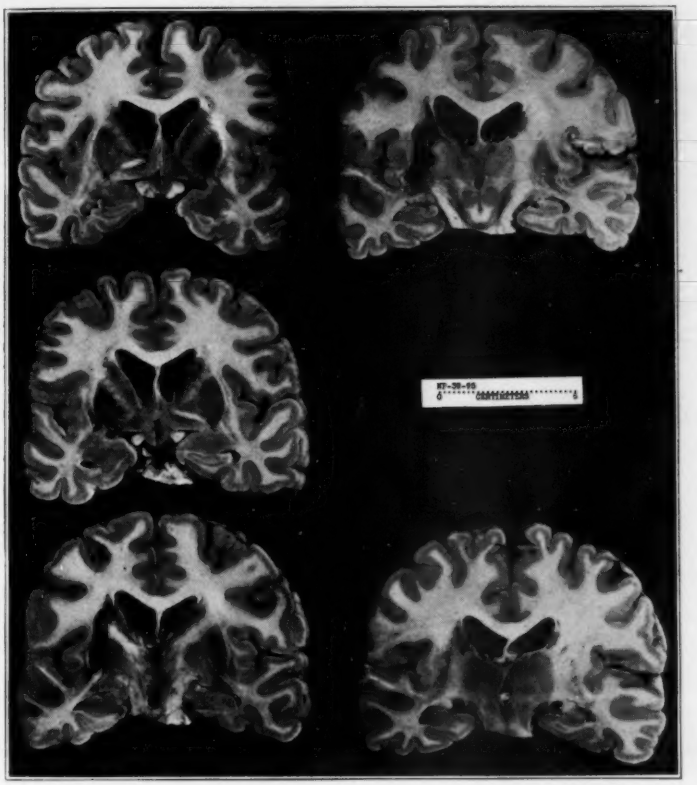

Fig. 3 (case 3).—Coronal sections, 6 mm. in thickness, of the cerebral hemispheres, to show the softening in the right hemisphere.

Coronal sections, 6 mm. in thickness, were made of the cerebrum (fig. 3). An old cystic area of softening destroyed the following structures on the right: the posterior and inferior portions of the claustrum and the external capsule; the posterior half of the putamen and of the internal capsule, and the posterior tip of the caudate nucleus. The thalamus was intact, but the right thalamocortical radiations appeared to have been completely interrupted. There was slight dilatation of the right lateral ventricle in the sections containing the softening.

The lesion was irregularly cystic. The walls of this cyst were lined with a golden brown, filmy membrane, the cavity being separated into numerous divisions by strands of the weblike tissue.

The basal ganglia of both hemispheres and representative sections of the brain stem and spinal cord were taken for studies of the myelin sheaths.

CLINICAL SUMMARY

The salient clinical facts in the 10 cases of flaccid hemiplegia are summarized in the accompanying table. A few points need clarification. The age listed is that at the time of onset of the flaccid paralysis. Duration of the flaccidity is the verifiable duration (up to June 1, 1939, or

Tabulation of the Salient Facts in Ten Cases of Permanent Flaccid Hemiplegia

Case No.	Age at Onset	Duration of Flaccidity	Ocular Signs	Motor Signs	Sensory Signs†	Present Status
1	65	4 mo.	Left hemianopia ?	Left hemiplegia; global aphasia	Could not be tested	Died; autopsy
2	48	5 mo.	Right hemianopia	Right hemiplegia; atrophy +++; global aphasia	Some loss; could not be tested	Died; autopsy
3*	43	22 mo.	Visual inattention in left field; objects brighter in right (normal) field	Left hemiplegia; atrophy +++	Marked diminution in all forms; cortical loss	Died; no autopsy
4	67	14 mo.	Right hemianopia	Right hemiplegia; some receptive aphasia	Some cortical loss	Hospital
5	53	11 mo.	None	Left hemiplegia; atrophy +	Cortical loss	Hospital
6	67	7½ mo.	None	Left hemiplegia; atrophy +	Cortical loss	Died; autopsy
7*	35	7½ yr.	Visual inattention in left field	Left hemiplegia; atrophy ++; convulsions of right side only	Profound loss	Invalid at home
8	48	2 mo.	Occlusion of left retinal artery; could not be tested	Right hemiplegia; global aphasia	Could not be tested; terminal thalamic pain	Died; no autopsy
9	32	1 mo.	None	Left hemiplegia	Cortical loss	Died; no autopsy
10	52	4 mo.	Left hemianopia	Left hemiplegia	Cortical loss	Hospital

* Traumatic in origin.
† Since the preparation of this paper a patient has been observed with flaccid hemiplegia (left) of four months' duration, without any demonstrable loss of sensation.

until death). In all cases but 1 the patient was observed shortly after the most recent ictus. In the 1 case in which the patient was not observed at the onset (case 7) there are authentic records which leave little doubt of the time of onset. This patient had been repeatedly examined by neurologists since the onset seven and a half years before. In 5 cases there was aphasia, usually of extreme severity, and in all instances in which sensation could be tested there was a severe defect.

The patient with flaccid hemiplegia is severely crippled. The paralysis is as conspicuous in the muscles of the hip and shoulder girdles as it is in the more distal musculature. Two of these 10 patients

regained the ability to walk; the others remained bedfast, or were confined to bed until death. The 2 patients who are able to walk have regained some strength in the quadriceps muscle. One patient brings the paralyzed limb forward by inserting a cane between the thighs and using it as a lever. By pressure of the cane against the anterior surface of the normal thigh he is able to drag the paralyzed limb forward. The paralyzed limb abducts, and the foot drags on the floor during this maneuver. He then places all his weight on the cane, which is in his sound hand, and brings the normal lower limb forward. He has become dextrous in these movements and progresses at a fair rate. This patient (case 7) is 42 years of age and has had paralysis for seven and a half years. When he is in a reclining position one is unable to demonstrate any voluntary movement in the affected limbs or their girdles. The remaining patient (case 5) who is able to walk has regained a slight amount of strength in the quadriceps muscle, and his gait is much like that which was just described. Verhaart's [2] opinion that prolonged flaccid paralysis is a poor prognostic sign as far as some recovery of movement is concerned is probably valid.

REVIEW OF LITERATURE

There has been some record of flaccid paralysis in man in the literature. The most valuable and recent writing is that of Verhaart,[2] who reported 5 cases of flaccid hemiplegia. He made serial sections of the basal ganglia and brain stem of these patients and concluded that a lesion of the pyramidal tract accompanied by damage to the lateral thalamic nucleus results in flaccid hemiplegia. He expressed the opinion that interruption of the mesial fillet and superior cerebellar peduncle is important in the production of flaccidity. He noted that long-standing flaccid hemiplegia had been present in the face of extensive cerebral lesions, combined with lesions of the basal ganglia and other, more deeply situated structures. He expressed belief that flaccid hemiplegia in man indicates that the prognosis is poor. In 3 of Verhaart's cases there were lesions of the striatum. Of the 2 in which there were no striatal lesions 1 was that of a man aged 65 who had had right hemiplegia since birth. The lesions in the central nervous system of this patient were: atrophy of the white matter of the left frontal, parietal and occipital lobes, with enormous dilatation of the left lateral ventricle; degeneration of the left internal capsule between the anterior pole of the thalamus and the putamen; diminution in the size of the dorsal portion of the lateral thalamic nucleus, which contained many areas of

2. Verhaart, W. J. C.: Flaccid Hemiplegia of Cerebral Origin, Psychiat. en neurol. bl. **41**:211-217, 1937.

gliosis and showed loss of nerve cells; atrophy of the mesial fillet and superior cerebellar peduncle to one half the size of those on the right; disappearance of the lateral half of the frontopontile tract in the left peduncle; diminution in size of the gracile and cuneate nuclei on the left and of the dentate nucleus on the right and demyelination of both columns of Goll in the spinal cord. The other case in which there was no involvement of the striatum was that of a man aged 55 who had had left flaccid paralysis for six months. The changes in the nervous system were described.

> There was a relatively extensive focus in the lateral thalamic nucleus and the adjacent internal capusle and comb system [Edinger's *Kammsystem*, the ansa lenticularis and the hypothalamic lenticular fasciculus—field H_2 of Forel], that continued as far as the latero-frontal radiation of the red nucleus without involving the nucleus itself.

In the internal capsule and peduncle only the pyramidal area was degenerated.

Niessl von Mayendorf [3] reported 4 cases of flaccid hemiplegia in which autopsy was performed. He stated that the postcentral convolution (areas 3, 1 and 2) "transmitted tonic impulses," for the sensory pathways (lateral thalamic nucleus, lemniscus in the pons, thalamocortical radiations) were involved somewhere in all of them, although in his cases there were widespread lesions in the cortex and basal ganglia.

Davison and Bieber,[4] studying flaccidity and spasticity in man in the light of work of Fulton and his group (see recent publications [4a]), found that the premotor area (area 6) in man may be involved without giving rise to spasticity, and also that the integrity of the premotor area is not solely responsible for the presence of flaccidity. They recorded 6 cases, with autopsy, in which the middle cerebral artery had been completely or partially occluded and in which there had been enduring flaccidity. Autopsy in these cases had revealed softening of the cortex and of the basal ganglia supplied by the middle cerebral artery. This report does not contain a detailed description of the destruction in the basal ganglia. Destruction of the putamen and portions of the globus pallidus and external capsule is mentioned in 2 cases. In the other cases involvement of the basal ganglia is implied.

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3. Niessl von Mayendorf, E.: Sur la combinaison de la paralysie musculaire flasque d'origine cérébrale avec une exagération des réflexes tendineux, Rev. neurol. **65**:1265-1272, 1936.

4. Davison, C., and Bieber, I.: The Premotor Area: Its Relation to Spasticity and Flaccidity in Man, Arch. Neurol. & Psychiat. **32**:963-972 (Nov.) 1934.

4a. Fulton, J. F.: Physiology of the Nervous System, New York, Oxford University Press, 1938, p. 675; footnote 1.

COMMENT

The work bearing on the problem of flaccidity and spasticity can be most simply presented by a diagram (fig. 4). After analysis of the work on flaccidity and spasticity in man and animals and the results of studies of human pathologic material, it appears that the important

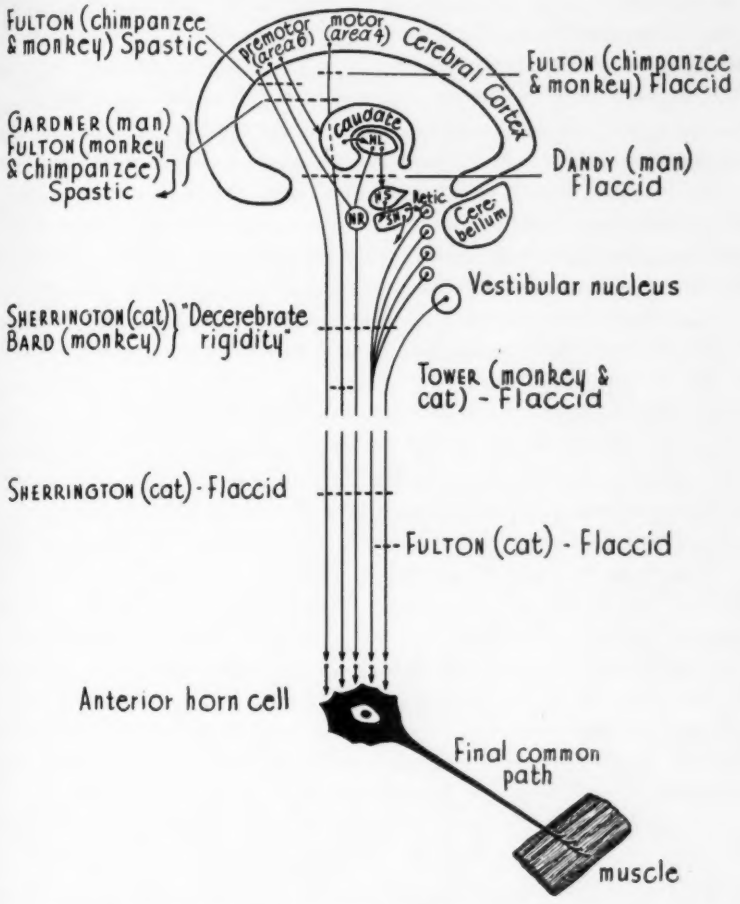

Fig. 4.—Diagram of the motor system (modified from Cobb, S.: A Preface to Nervous Disease, Baltimore, William Wood & Company, 1936, page 38), to illustrate the effect of ablation and section of various areas of the nervous system. *N L* indicates the lenticular nucleus; *N R*, the red nucleus; *N S*, the subthalamic nucleus; *S N*, the substantia nigra, and *Retic*, the reticular formation.

structures usually determining the nature of the paralysis associated with cerebral lesions in man are the basal ganglia. The decisive work on the question consists of the hemispherectomies and hemidecortications

performed by Dandy [5] and Gardner [6] in man, and by Walker and Fulton [7] in the chimpanzee. Hemidecortication in the hands of Gardner and Walker and Fulton produced a spastic result, while Dandy obtained long-standing flaccid paralysis in 2 patients on removing the hemisphere. Study of the protocols and case histories involved in this work reveals, I think, the reason for these seemingly conflicting results. The crux of the matter appears to be the method by which the blood supply was handled by the various operators. Dandy first exposed the main blood supply to the cerebral hemisphere of his 2 patients by elevating the frontal lobe, and on one occasion he separately clipped and divided the anterior, middle and posterior cerebral arteries. In the second case he doubly clipped and divided the internal carotid artery and then immediately doubly clipped and divided the anterior and middle cerebral and the posterior communicating arteries. He noted in one of his protocols that the tension of the brain was much reduced by the exclusion of arterial blood, and in the other that the volume of the cerebral hemisphere was reduced markedly, and at once, by this procedure. In the second case Dandy obstructed the posterior cerebral supply as he extirpated the mass of the hemisphere.

In both these cases it seems fair to assume from Dandy's clear report that most of the blood supply of the basal ganglia was removed and that, despite the fact that the basal ganglia were left intact as far as extirpation was concerned, they were functionless, owing to loss of their blood supply. The great part of the arterial supply to the basal ganglia is derived from branches of the middle cerebral artery. The anterior cerebral artery supplies a portion of the most rostral tip of the caudate nucleus, and it is possible that this supply escaped, depending on the position of the clips on that vessel, granted that there was a functioning anterior communicating artery. The posterior cerebral artery, the proximal portion of which probably was spared in Dandy's second case, is of no importance in the supply of the striatum. The preservation of some sensation in each of Dandy's 2 cases must be explained. In the first case, in which the anterior, middle and posterior cerebral arteries were cut, the only supply to the thalamus then could be from the posterior communicating artery. Perforating thalamic arteries arise from this vessel to supply the anterior and medial portions of the thalamus (Walker [8]). Possibly the posterior mesial ganglionic arteries from the

5. Dandy, W. E.: Physiological Studies Following Extirpation of Right Cerebral Hemisphere in Man, Bull. Johns Hopkins Hosp. **53**:31-51, 1933.

6. Gardner, W. J.: Removal of Right Cerebral Hemisphere for Infiltrating Glioma: Report of a Case, J. A. M. A. **101**:823-826 (Sept. 9) 1933.

7. Walker, A. E., and Fulton, J. F.: Hemidecortication in Chimpanzee, Baboon, Macaque, Potto, Cat and Coati: A Study in Encephalization, J. Nerv. & Ment. Dis. **87**:677-700, 1938.

8. Walker, A. E.: The Primate Thalamus, Chicago, University of Chicago Press, 1938, p. 321.

posterior cerebral artery, which enter the cerebral substance via the posterior perforated space, may have escaped. In the second case the posterior cerebral artery was cut lateral to the basal ganglia, so it is evident that most of the blood supply to the thalamus was intact in this patient.

In the hemidecortications performed by Gardner and Fulton, the midline veins to the sagittal sinus were cared for first, and the hemisphere was then retracted laterally. These operators secured the arteries to the hemisphere with clips and severed these vessels as they came across them in peeling away the cortex from the basal ganglia. Thus, they occluded the anterior, middle and cerebral arteries at points lateral to the basal ganglia, and by this maneuver they preserved the blood supply to these structures.

If these deductions are correct, they complement the results of postmortem examination of patients who exhibited prolonged flaccidity, and in whom the lateral portion of the striatum was destroyed, as well as the posterior portion of the internal capsule and the external capsule.

Whether one obtains a flaccid or a spastic result after removal of a hemisphere, or a portion of it, for tumor of the brain is of some importance. Some hold the opinion that this method offers the best result in treatment of gliomas of the cerebrum at present. Gardner's patient, who became spastic after hemidecortication, was able to walk with the aid of a cane. She lived somewhat happily for over two years, until she died as the result of an intracranial hemorrhage, caused by a fall. Gardner attributed her ability to walk to the function of the intact basal ganglia.

Experiments with chimpanzees are now under way in an attempt to elucidate the problem, after removal of the cortex of one hemisphere and after removal of an entire hemisphere.

SUMMARY

Clinical and pathologic studies in man indicate that destruction of portions of the basal ganglia together with portions of the external and internal capsules may result in prolonged flaccid paralysis.

The occurrence of flaccidity in man usually appears to depend on the destruction of the striatum and its radiations.

It is thought that the method of removing the hemisphere for glioma by first attending to the venous drainage before extirpation, and clipping the large arteries as they are brought into view, offers the best clinical result because it spares the blood supply to the basal ganglia, although this method is probably more difficult and dangerous than that of first removing the arterial circulation.

EVALUATION OF METRAZOL SHOCK IN TREATMENT OF SCHIZOPHRENIA

REPORT OF RESULTS IN ONE HUNDRED CASES

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While many papers have appeared recently in medical literature on the use of metrazol shock therapy of schizophrenia, the desirability of this method is far from settled, and therefore the report of results in large groups of patients still seems to be warranted. Because this method is so drastic, it is important to determine if its use is justified by the results obtained. Improvement in the mental condition of psychotic patients has been known to occur after severe physical illness. It is essential to learn if convulsive shock therapy is anything more than a series of attacks of physical illness administered in a highly effective manner with an extreme degree of severity. Prior to the use of shock therapy, different state institutions reported extremely varied results in the routine institutional treatment of schizophrenia. When individual and extensive therapy could be applied, the results were gratifying. Cheney and Drewry,[1] in a study of 500 schizophrenic patients who did not receive any so-called specific therapy but were treated by intensive, modern psychiatric methods, came to the following conclusions:

> Of a large group of dementia praecox patients of average or higher intelligence admitted to a hospital equipped and manned to give intensive, individual care and treatment by well established methods, and remaining for treatment for approximately one year, it may be expected that at the end of their hospital residence, 27 per cent of the total number will have benefited by treatment and 7 per cent will have recovered.

In the past, some reports of results obtained with metrazol shock therapy have been extremely enthusiastic,[2] others cautious and still

1. Cheney, C. O., and Drewry, P. H., Jr.: Results of Non-Specific Treatment in Dementia Praecox, Am. J. Psychiat. **95**:203 (July) 1938.

2. von Meduna, L.: The Convulsive Therapy of Schizophrenia, Psychiat.-neurol. Wchnschr. **37**:317 (July 6) 1935. Krüger, L.: The Treatment of Schizophrenia by von Meduna's Method, ibid. **38**:135 (March 21) 1936. Wahlmann: The Treatment of Psychosis with Metrazol, ibid. **38**:78 (Feb. 15) 1936. Friedman, E.: Irritative Treatment of Schizophrenia (Review of Twenty Cases), Am. J. Psychiat. **94**:355 (Sept.) 1937. Finkelman, I.; Steinberg, D. L., and Liebert, E.: The Treatment of Schizophrenia with Metrazol by the Production of Convulsions, J. A.

(Footnote continued on next page)

others indecisive. Perhaps the variation in the observations of different authors was caused by the difference in the stages of progress of the schizophrenic illness in their patients. This was especially true of patients in psychopathic wards of general hospitals, where patients with psychosis of recent onset were brought for a short period of observation, prior to commitment to state institutions. Some of these patients after receiving metrazol shock therapy achieved a "temporary remission," and when a few months later they had a recurrence of the symptoms they were not returned to the same hospital. County and state institutions, dealing chiefly with committed patients and serving a definite geographic area, are in a better position to observe the patient after discharge from the mental hospital, since, in case of relapse of the psychotic condition, the patient is usually returned to the same institution. Also, these institutions keep the patient on parole for a year after he leaves the hospital, and therefore are in closer contact with former patients, thus having opportunity for a frequent check-up through the social service department.

The present report deals with results obtained in the treatment with metrazol shock of 100 schizophrenic patients at the Hudson County Hospital for Mental Diseases. This study includes only patients in whose cases there was not the slightest doubt as to the diagnosis of schizophrenia. Every patient selected for the therapy was presented at a staff conference prior to administration of treatment and after completion of it to evaluate as accurately as possible the changes that took place. This avoided dependence on the impression of individual physicians, since no doubt the personality of different workers plays an important part in the proper evaluation of the effectiveness of the therapy.

PROCEDURE

Each patient was submitted to a preliminary check-up, which consisted of complete physical and neurologic examinations, roentgenographic studies of the chest, an electrocardiographic test, examination of the blood and other tests that might be indicated. Patients with advanced arteriosclerosis, hypertension, heart disease, organic neurologic diseases and bony deformities, especially ankylosis of large joints, were eliminated. Convulsive seizures were induced three times a week by intravenous injections of a 10 per cent aqueous solution of metrazol; the initial dose consisted of 3 to 4 cc., depending on body weight. If the first injection failed to induce a convulsive seizure of grand mal type, another injection was given in fifteen minutes; this was done because of the observation that patients who failed

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M. A. **110**:706 (March 5) 1938. Reese, H. H.; Vander Veer, A., and Wedge, A. H.: The Effect of Induced Metrazol Convulsions on Schizophrenic Patients, J. Nerv. & Ment. Dis. **87**:570 (May) 1938. Pamboukis, G., and Tsiminakis, J.: Cardiazol Treatment in Schizophrenia, Encéphale **2**:94 (July-Aug.) 1938. Beckenstein, N.: Results of Metrazol Therapy in Schizophrenia, Psychiatric Quart. **13**: 106 (Jan.) 1939. von Meduna, L., and Friedman, E.: Convulsive-Irritative Therapy of the Psychoses: Survey of More Than Three Thousand Cases, J. A. M. A. **112**: 501 (Feb. 11) 1939.

to react to the first injection with a grand mal seizure usually became disturbed later in the day, and often experienced extreme fear and anxiety and became panicky when the next injection had to be made; no untoward results were observed from this procedure. The dose was gradually increased by from 0.5 to 1 cc., since most patients gradually acquire tolerance to metrazol; the largest dose used with this group of patients was 14 cc. Lately the initial dose has been raised to 5 cc., to avoid undesirable incomplete reactions. The injection was made with a large needle, gage 18 or 19, as rapidly as possible.

Half the patients received sodium bicarbonate during the treatment for alkalization, but no advantages were noted from this procedure and it was later discontinued as unnecessary. Extensive blood pressure and electrocardiographic studies were made before, during and after the treatment, and will be reported on in a separate paper.

A total of 2,697 injections of metrazol were made, of which 2,087 resulted in seizures of grand mal type.

Of the 100 patients, 53 were men and 47 women. The oldest patient was 44, the youngest, 17. Most of the patients gained weight; a few lost weight; it was noticed that patients who reacted poorly to this treatment usually either gained little weight or lost a few pounds; for the whole group, the average gain in weight amounted to 9.14 pounds (4.16 Kg.).

In general, patients were submitted to from 15 to 20 convulsive seizures, although in the beginning of this study patients who failed to show improvement were given as many as 35 to 40 treatments in the hope that some improvement might result; later this practice was abandoned, since it was noticed that if improvement did not result after 20 or 25 grand mal seizures further administration of shock treatment was useless; in some patients satisfactory results were obtained with 10, or even 5, injections of metrazol.

It is difficult to determine with any degree of accuracy the duration of psychotic illness; statistical reports of results obtained by various workers may be influenced tremendously by the type of patients treated; obviously, opportunity for improvement is greater in cases of mild illness of short duration than in those of chronic, deteriorated states in which the illness has lasted for a number of years. The longest duration of psychosis among the patients in this group was fifteen years, the shortest, five weeks; the average duration was thirty-four and four-tenths months. According to the duration of the psychosis, the cases were divided into four groups:

Duration	No. of Cases
Under 6 months	26
6 months to 2 years	26
2 years to 5 years	32
Over 5 years	16

The cases were also classified as to the type of schizophrenia, in this manner:

Type	No. of Cases
Catatonic	24
Paranoid	38
Hebephrenic	31
Simple	3
Unclassified or mixed	4

The treatment lasted from two weeks (when only 5 grand mal seizures were induced) to seventeen weeks in some cases; on the average, treatment was continued for eight weeks

RESULTS

Results of treatment were designated by the terms "apparent remission," "much improved," "improved," "slightly improved" and "not improved." The term "apparent remission" was used when, at the time of parole, the patient was entirely free from psychotic symptoms, had insight into his past psychotic difficulties and was capable of being occupied in the work in which he was engaged prior to development of the psychosis. It was used in this study in preference to the term "recovery" because the duration of so-called metrazol recoveries is still unknown and relapses are frequent. The term "much improved" was used when the patient did not manifest any hallucinations or delusions, but still showed some emotional inadequacy. These patients were capable of doing their previous work. The term "improved" was applied to patients whose behavior was good, although they manifested some mild psychotic symptoms and defects in the emotional field. These patients could make adjustments outside the hospital only with the help of their families and friends. All patients in the preceding three groups were eligible for parole. The patients designated as "slightly improved" and "not improved" were not considered eligible for parole. The patients who were "slightly improved" showed some improvement in behavior, but had hallucinations and delusions and were emotionally shallow. These patients, because of improvement in behavior, made better institutional patients but could not be expected to engage in gainful occupation outside the hospital. Some of these patients before treatment with metrazol was started had had to be fed with a tube and were slovenly and destructive, but after the therapy became more cooperative, at least for a few months. In the group who were "not improved" were included patients whose mental condition did not show any change after the therapy was completed. In the final analysis, it was decided to combine the groups showing slight improvement and no improvement, since this helped considerably in maintaining statistical records and since, after all, there was only a slight degree of difference in psychotic behavior and in ability for institutional adjustment, which frequently was only temporary; many of the patients who did not show improvement were deteriorated.

When the treatment was completed, and before the patients were considered for parole, the results for the group were recorded as follows:

	No. of Patients
Apparent remission	24
Much improved	12
Improved	8
Slightly improved or not improved	56

However, as time has passed some of the patients who achieved apparent remission or improvement gradually have shown symptoms of relapse to their former state, and therefore the figures have had to be constantly revised. When this paper was prepared, some of the patients who showed improvement had been away from the hospital for over a year, others for only three months; on the average, for the group as a whole seven months had elapsed since treatment was completed. As there is a definite tendency to relapse, the percentage of patients exhibiting improvement doubtless will be much smaller a year from now, and will gradually decrease with time.

As seen from table 1, of 24 patients who achieved apparent remission 6 suffered a relapse; 5 of the patients who were much improved and 1 of those who were improved had relapses, making a total of 12

TABLE 1.—*Results of Treatment According to the Duration of Schizophrenia*

Duration of Psychosis	No. of Patients	Patients with Remissions		Patients Much Improved		Patients Improved		Patients with Relapses		Patients Not or Slightly Improved	
		No.	%	No.	%	No.	%	No.	%	No.	%
Under 6 mo.....	26	12	46.1	5	19.3	4	15.4	4	15.4	5	19.3
From 6 mo. to 2 yr.	26	8	30.8	2	7.7	3	11.6	5	19.3	13	50.0
From 2 to 5 yr.....	32	3	9.4	4	12.5	1	3.1	2	6.3	24	75.0
Over 5 yr.....	16	1	6.3	1	6.3	..	....	1	6.3	14	87.5
Total.....	100	24		12		8		12*		56†	

* Twelve patients in the three groups showing improvement had relapses after being on parole from three months to one year.

† Fifty-six patients did not improve after treatment was completed and before parole, while three months to a year later the number of patients who showed no improvement was increased by 12 with relapses, making a total of 68 who were not improved.

relapses. Six of the patients with a relapse have been returned to the hospital, while the families of the remaining 6 patients are reluctant to return the patients to the hospital, although check-up leaves no doubt that the patients are regressing. Among the 16 patients with psychosis of over five years' duration, only 1 (6.3 per cent) achieved an apparent remission, 1 was considered as much improved (6.3 per cent) and 14 (87.5 per cent) showed no improvement whatever. It is interesting to note that the 1 patient who achieved remission had had a psychosis of thirteen and a half years' duration, but had been hospitalized for only thirty-three months, on five different occasions, since he had had in the past a definite tendency to spontaneous remissions. In general, it was my observation that when a careful study of the past history showed periods of remission and gainful employment, the patient had a better chance of improvement with shock therapy than when the history indicated continuous, uninterrupted progress of schizophrenia.

The tendency to relapse is greater in cases of illness of long duration than in those of recent onset; so far only 1 patient who had been ill less

than six months has had a relapse, while in the other two groups 11 (23.4 per cent) of the patients showing improvement had a relapse. Two of the patients with a relapse were given a second course of metrazol treatment; both were catatonic, mute and negativistic and refused food on the first admission; both made a "dramatic recovery" with metrazol therapy, were paroled and had a relapse eight months later; on readmission they again presented the same psychotic picture: negativism, mutism, refusal of food and catatonic rigidity. The second course of metrazol injections helped to bring them out of the catatonic state; they are now cooperative and well behaved, but any experienced psychiatrist can see that they lack spontaneity and initiative, and are emotionally shallow; they could perhaps return to their former positions for a short period; they certainly are better fitted to be employed in the

TABLE 2.—*Results of Treatment According to the Type and Duration of Schizophrenia, Including Relapses*

	Catatonic				Hebephrenic				Paranoid				Simple				Unclassified			
	Under 6 Mo.	6 Mo. to 2 Yr.	2 Yr. to 5 Yr.	Over 5 Yr.	Under 6 Mo.	6 Mo. to 2 Yr.	2 Yr. to 5 Yr.	Over 5 Yr.	Under 6 Mo.	6 Mo. to 2 Yr.	2 Yr. to 5 Yr.	Over 5 Yr.	Under 6 Mo.	6 Mo. to 2 Yr.	2 Yr. to 5 Yr.	Over 5 Yr.	Under 6 Mo.	6 Mo. to 2 Yr.	2 Yr. to 5 Yr.	Over 5 Yr.
Patients with remissions	3	3	..	..	..	..	2	..	5	2	1	..	1	..	..	1	..	..	..	..
Patients much improved	1	..	..	..	1	1	1	..	2	..	..	..	..	..	..	..	..	..	1	..
Patients improved	1	..	..	..	2	2	..	..	1	..	..	..	..	..	..	..	..	..	1	..
Patients not improved or slightly improved	7	4	4	1	1	6	8	7	1	7	14	5	..	..	..	1	1	..	..	1

occupational therapy department of the hospital, but the essential schizophrenic pattern remains unaffected by metrazol therapy. All that is in favor of metrazol therapy in these 2 instances is that on admission the patients were entirely inaccessible; now they are accessible and in a more cooperative state for occupational and recreational therapy or psychotherapy.

While patients with catatonia of short duration react well to metrazol shock therapy after a few injections, they do not seem to maintain improvement long and present more relapses than the paranoid group.

Table 2 gives the results for each type of schizophrenia.

COMPLICATIONS

Many complications have been reported, including such diverse conditions as fractures of the spine, clavicle, jaw, long bones[3] and pelvis;

3. Somers, D. C., and Richardson, R. P.: Bilateral Fracture of the Femoral Necks Caused by Metrazol Convulsions (Report of a Case), Am. J. Psychiat. **95:** 1193 (March) 1939.

dislocations of the mandible, shoulder and other joints, and aspiration of fluid (during the vomiting, which at times follows the convulsion) with resulting lung abscess [4] or pneumonia. A few fatalities have also been reported.[5] In this group of 100 patients 83 temporomandibular dislocations occurred in 14 patients. Some patients had dislocations of the jaw on several occasions; 1 patient had 20 grand mal seizures, and each time his lower jaw was dislocated; apparently, relatively weak or relaxed ligaments were responsible for this occurrence. Dislocations of the jaw were easily reduced when the seizure subsided, and often the jaw snapped into place when the convulsion ceased. One patient had an incomplete fracture of the left scapula. There were no deaths.

Because of recent reports [6] of frequent fractures of the vertebrae, at times without any subjective complaints or physical signs, it has been decided that at this hospital roentgenograms are to be made in the future of the spinal column prior to and after completion of the treatment. It seems that with extreme caution, and in experienced hands, complications may be reduced to a minimum: If the extremities are directed toward the midline, fractures and dislocations of long bones may be avoided in many cases. If the treatment is given on an empty stomach, chances for aspiration of fluid during vomiting may be reduced; a tongue depressor covered with gauze should be inserted between the teeth to prevent biting the tongue. Patients should remain in bed for a few hours after the injections of metrazol.

SUMMARY AND CONCLUSIONS

One hundred schizophrenic patients have been treated with metrazol; there were 53 men and 47 women, ranging in age from 17 to 44; the duration of schizophrenia varied from five weeks to fifteen years, the average period being thirty-four and four-tenths months. A total of 2,697 injections were made. Patients had from 5 to 40 convulsive seizures of the grand mal type. There were 83 dislocations of the mandible and 1 fracture of the scapula; there were no deaths.

When the treatment was completed, 44 per cent had improved, and 56 per cent were not improved. At present, three months to a year after completion of therapy (average seven months), 32 per cent are improved, and 68 per cent are not improved.

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5. Hayman, M., and Brody, M. W.: Metrazol Therapy in Schizophrenia: Report of a Fatal Case with Autopsy, J. A. M. A. **112**:310 (Jan. 28) 1939.

6. Polatin, P.; Friedman, M. M.; Harris, M. M., and Horwitz, W. A.: Vertebral Fractures Produced by Metrazol-Induced Convulsions in the Treatment of Psychiatric Disorders, J. A. M. A. **112**:1684 (April 29) 1939.

There is a definite and persistent tendency to relapse in patients treated with metrazol shock therapy.

Catatonic patients with psychosis of short duration react in the most "dramatic" way to a few injections of metrazol, but catatonic patients always have been more apt to have remission.

Improvement is maintained longer in paranoid than in catatonic patients.

Metrazol shock therapy aids in achieving remissions earlier than routine treatment, thus reducing the duration of hospitalization; the method is convenient and economical.

Metrazol shock therapy may be utilized in preparing uncooperative, inaccessible patients for other therapeutic measures, such as occupational and recreational therapy and psychotherapy.

Metrazol shock therapy is of little or no value for patients with psychosis of long duration, unless previously they have shown a tendency to spontaneous remission.

Patients with psychosis of long duration with definite, marked deterioration fail to show any improvement; at best, they become "better institutional patients," and even then for only a short time.

Metrazol shock therapy does not seem to produce permanent and lasting recovery.

It is my impression that, while amelioration of psychotic symptoms occurs in many patients, the essential schizophrenic pattern remains unchanged.

The staff of the hospital gave valuable assistance and cooperation in carrying out this work.

PRODUCTION AND LOCALIZATION OF HEADACHE WITH SUBARACHNOID AND VENTRICULAR AIR

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"Arterial" experimental headaches have been produced by intravenous and intra-arterial injections of histamine phosphate [1] and by direct electrical and mechanical stimulation of the larger cerebral and meningeal arteries at operation.[2] "Dural" headaches have been produced by mechanical, electrical and thermal stimulation of the dura during craniotomy.[3] "Pressure" headaches have been produced by sudden alterations of intracranial pressure.[4]

Although it is common surgical knowledge that the brain and its leptomeninges are insensitive to mechanical, electrical and thermal stimuli, both ventriculography and encephalography are painful procedures. The former causes only mild discomfort,[4b, c] but encephal-

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2. Fay, T.: Mechanism of Headache, Tr. Am. Neurol. A. **62**:74, 1936; Arch. Neurol. & Psychiat. **37**:471 (Feb.) 1937.

3. Penfield, W.: A Contribution to the Mechanism of Intracranial Pain, A. Research Nerv. & Ment. Dis., Proc. **15**:399, 1934. Northfield.[1c]

4. (*a*) Masserman, J. H.: Cerebrospinal Hydrodynamics: Clinical Experimental Studies, Arch. Neurol. & Psychiat. **32**:523 (Sept.) 1934. (*b*) Brewer, E. D.: Etiology of Headache: Occurrence and Significance of Headache During Ventriculography, Bull. Neurol. Inst. New York **6**:12 (Jan.) 1937. (*c*) Northfield.[1c]

ography causes severe localized, referred and, finally, generalized pain. Alterations of intracranial pressure occur in both ventriculography and encephalography. Air acts as an irritant on the ventricular walls in both. In encephalography additional irritation occurs by exposure of the main vascular channels and leptomeninges to the air. The headache due to encephalography has been studied by Elsberg and Southerland, who concluded that it was a result of alterations in pressure caused by the presence of air in the third and lateral ventricles.[5]

A modification of encephalography was devised in which the intracranial pressure is kept fairly constant while small air bubbles are introduced into various parts of the ventricular and subarachnoid systems. The purpose of the experiment is to correlate the headache with the location of the irritant focus. Independently developed in this clinic in 1934, this method differs from that used by Elsberg in that there is no withdrawal of cerebrospinal fluid until after headache has been produced, much smaller amounts of air are introduced and the intracranial pressure is kept fairly constant.

METHOD

A subject who is a reliable witness is seated erect with a Potter-Bucky roentgen casette supported vertically behind his head. A roentgen apparatus is set up before him and prepared for an anteroposterior stereoscopic exposure. The subject's head is placed in such a position that a bubble of air ascending from the lumbar subarachnoid space will tend to lodge in some predetermined intracranial position. Such positions are in turn determined by consideration of the ventricular and subarachnoid anatomy. A lumbar puncture is performed with aseptic technic; no fluid is removed, and the pressure is measured with the ordinary open end spinal fluid manometer. The subject is told to remain as placed, immediately to report any pain and to localize and describe it. From 1 to 2 cc. of room air is rapidly injected into the lumbar subarachnoid space. If no pain is reported, the patient's head is gently shaken. If no pain results, the injections are continued until it does. When pain occurs stereoscopic anteroposterior and lateral exposures are made without changing the position of the subject's head. The lumbar cerebrospinal fluid pressure is now rechecked and, if significantly elevated, is reduced by withdrawal of cerebrospinal fluid. The position of the bubble is then shifted by moving or shaking the subject's head. If a new symptom occurs or if the pain disappears, the roentgenograms are repeated in this new position.

The first of each stereoscopic set is centered and the second taken with a 5 inch (12.7 cm.) shift at a distance of 30 inches (76.2 cm.), a 58 kilovolt potential and 15 milliamperes for six seconds being used for anteroposterior exposures, and a 54 kilovolt potential and 15 milliamperes for five seconds for lateral exposures. The casette should run for seven to eight seconds for each. Lateral placement of the bubble is best performed with the patient in the upright position and the head tilted toward the shoulder. Variations in cranial posture are innumerable. No untoward reactions have occurred in our series.

5. Elsberg, C. A., and Southerland, R. W.: Etiology of Headache: Headache Produced by Injection of Air for Encephalography, Bull. Neurol. Inst. New York **3**:519 (March) 1934.

RESULTS

Headache was produced by the technic described in 20 subjects. In the first 6 cases nothing was done to change the initial headache. In another 6 cases an attempt was made to alter the headache by shaking the head or changing its position. In 2 of these the initial headache disappeared after shaking; in 2 it shifted from anterior to posterior frontal; in 1 it changed from bifrontal to left temporal, and in another it was unaltered. In the remaining 8 cases an attempt was also made to alter the headache, and, in addition, a second set of roentgenograms was made after shaking the head.

Volume of Air.—From 2 to 16 cc. of air was needed to produce headache. Two cubic centimeters was sufficient in 2 cases; 3 cc. in 2 cases; 4 cc. in 3 cases; 5 cc. in 1 case; 6 cc. in 3 cases; 7 cc. in 1 case; 8 cc. in 2 cases; 9 cc. in 1 case; 10 cc. in 2 cases, and 12, 13 and 16 cc. in 1 case each. Within these limits, the amount of air necessary to produce headache did not influence the location, degree or type of headache. It is of interest that, with the exception of 2 cases, in 1 of which there was air in both lateral ventricles and in the other

Relation of Cerebrospinal Fluid Pressure to Headache Produced by Small Volumes of Subarachnoid Air

Air Injected, Cc.	Lumbar Spinal Fluid Pressure, in Mm. Spinal Fluid*			Headache		
	Before Injection	After Injection	Difference in Pressure	Side	Location	Degree
6	410	480	70+	Left	Frontal	Dull
4	410	430	20+	Left	Frontal	Dull
5	480	480	0	Right	Temporal	Dull
8	500	490	10—	Bilateral	Frontal	Dull
4	555	540	15—	Right	Frontal	Dull
2	490	470	20—	Left	Frontal	Severe
4	480	460	20—	Bilateral	Frontal	Severe

* Measured while patient was in the sitting position.

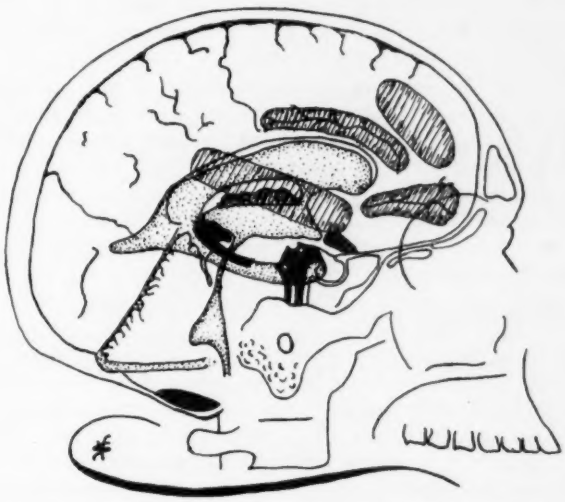
all the air was in the cisterna magna, not more than half the expected volume of air could be localized by roentgenographic estimation.

Cerebrospinal Fluid Pressure.—In 7 cases the lumbar cerebrospinal fluid pressure was measured with the patient sitting erect before and after the production of headache by the injection of air (table). The only fluid allowed to escape before these pressures were taken was that displaced into the spinal fluid manometer during the pressure reading. Three-hundredths of a cubic centimeter was displaced for each centimeter of rise in the manometer.

Apparently, the change of cerebrospinal fluid pressure caused by the introduction of from 2 to 8 cc. of air is an individual variant, unrelated to the amount of air injected. The reduction of pressure, in 4 cases, after the introduction of air is difficult to account for unless these patients were under less emotional (and postural) tension after the introduction of air. Judging from the patients' behavior, and from the fact that they had a headache during the second pressure reading, this is unlikely. This aspect of the observations remains unexplained. Nevertheless, the manometric readings clearly demonstrate that the headache produced by such small bubbles of air in the subarachnoid and ventricular spaces is not due to an increase in intracranial or intraventricular pressure. In no case was there any roentgenographic evidence of ventricular distention or distortion. In the single case in which there was a significant elevation of pressure (70 mm.)

reduction of the pressure to normal failed to alter the headache. The observation that the more severe headaches occurred with the greater decrease in pressure is probably merely coincidental in such a small group.

Sensitive Areas.—Unfortunately, introduction of small volumes of air into the lumbar subarachnoid space causes the air to be broken up, so that in only 4 cases was there a single, continuous bubble. Therefore, a process of elimination was necessary in determining which of several bubbles was responsible for the headache. In the 4 cases in which there was only a single bubble, air in the cisterna magna caused a severe generalized bilateral headache, in the cisterna interpeduncularis a dull bifrontal headache, in the cisterna ambiens (body and horns) a dull bifrontal headache and in the prechiasmatic and postchiasmatic cistern and the left horn of the cisterna ambiens a dull bifrontal and bitemporal headache. Therefore, from these observations alone, it might be assumed that the cisternae magna,



Areas capable of producing headache in man. In this drawing, black portions indicate definitely sensitive areas; lines, questionably sensitive areas (note roof of the third ventricle), and stippling, the insensitive ventricular system and the possibly sensitive subtentorial subarachnoid space.

interpeduncularis, prechiasmatica, postchiasmatica and ambiens (body and horns) are sensitive areas capable of producing referred headache on appropriate stimulation.

In 3 cases the bubbles were localized roentgenographically during an asymptomatic interval caused by shaking and moving the head. In these cases the initial headache disappeared for from ten to thirty minutes, later recurring in an altered form. Analysis of these cases showed that the air had in 1 case moved from the cisternae magna and pontis to the anterior third of both lateral ventricles. In another, it had moved from the upper portion of the fourth ventricle, the aqueduct, the anterior and posterior portions of the third ventricle, the left occipital horn, and the posterior third of both lateral ventricles to the entire body of the right lateral ventricle and the middle third of the body of the left ventricle, leaving merely a minute bubble in the anterior part of the third ventricle. In

the third case the air had shifted from the anterior third of the left lateral ventricle, the left horn of the cisterna ambiens, the prechiasmatic and postchiasmatic and interpeduncular cisterns and the left sylvian fissure to both lateral ventricles and the upper part of the cisterna interpeduncularis. Less air was seen in the sylvian fissure. In this case the headache rapidly returned. It is therefore suggested that, among others, the insensitive areas are: the bodies of the lateral ventricles, and possibly the horns of the cisterna ambiens, the upper part of the interpeduncular cistern and the anterior tip of the sylvian fissure.

In 5 other cases varying amounts of air appeared in the bodies of the lateral ventricles during headache, but in all of these there was also air in other areas. These were: the body of the cisterna ambiens (in 3 instances), the cisterna interpeduncularis, the postchiasmatic cistern and the superior part of the third ventricle (in 4 instances). All of these areas except the third ventricle had been demonstrated as sensitive areas in other cases. In 2 of these instances the only air observed was that in the third ventricle and in the bodies of the ventricles. If the lateral ventricles are insensitive it is, therefore, necessary to add the roof of the third ventricle to the list of sensitive areas.

In all but 1 of the remaining 8 cases the headache could be explained by the presence of air in these sensitive areas (as well as in other areas); in this case air in the supracallosal, cingulate and sylvian sulci caused bilateral headache. These might also be added to the presumably sensitive areas.

Air was seen in several other areas during headache, but always in conjunction with bubbles in the "'sensitive areas." It is not certain, therefore, whether these other foci are or are not sensitive. These foci were the cisterna pontis, the subtentorial subarachnoid space near the torcula and over the vertex of the vermis, the rostral sulci of the median surface of the frontal lobes and the antero-lateral sulci of the frontal region.

These experiments have demonstrated that in the unanesthetized human subject with an intact cranium, headache may be produced by local irritation of the structures lying in the cisterna prechiasmatica and postchiasmatica, interpeduncularis, magna and ambiens. They have also presented (less definite) evidence that the roof of the third ventricle and the supracallosal, cingulate, sylvian and (probably) frontal sulci are also sensitive areas. They have also shown that the ependymal surfaces of the lateral ventricles are probably insensitive to such local stimulation (figure).

Lateralization of Pain.—In the 3 cases in which the largest amounts of air were injected (10, 12 and 16 cc.) the resultant headache was generalized. In all the others it was lateralized or referred to certain areas. In 8 cases the headache was lateralized to the right or the left frontal area, and in 1 to the right temporal region. In only 1 of these cases was the air entirely homolateral with the pain. In 4 cases it was predominantly homolateral, in 3 in the midline and in 1 contralateral. More detailed analysis of these cases indicated that the presence of any air over the hemispheres caused lateralization of the pain to the side on which it was found. Air in the basilar cisterns, however, was accompanied by bilateral reference of the pain, or by lateralization to either frontal area, usually that homolateral with the preponderance of air. In all cases in which the patient lay on one side, the pain was lateralized to the uppermost half of the cranium.

Reference of Pain.—In all cases, except the 3 in which there was generalized headache, the bubbles of air caused reference of pain to areas at some distance from the irritant focus. In 2 cases pain was first appreciated in the posterior

cervical area, rapidly shifting to both temporal or the left frontal area. The roentgenograms taken during the second phase of the headache revealed the air to be in both temporal areas in the first case and predominantly in the left frontal region in the second. Possibly, the bubble had moved from a subtentorial to another position. On the other hand, subtentorial air seen in the cisterna magna, the fourth ventricle, over the cerebellar hemispheres or in the cisterna ambiens was not associated with pain in the cervical region or the posterior fossa. In only 1 case was the pain (temporarily) occipital, and here the air was in the postchiasmatic cistern and over the frontal part of the hemisphere. The present series of experiments indicate that bubbles of air over the hemispheres are often associated with local reference of pain, and that almost invariably the pain associated with irritation of the basal cisterns is referred deep behind the eyes or to the more superficial frontal or temporal areas.

Type of Pain.—In 4 of the 20 cases the headache was described as "severe," in the remainder as "dull." The severity of the pain was unrelated to the volume of air injected (2, 4, 6 and 10 cc.), to the intracranial pressure or to the location of either pain or air. Two of the patients with severe headache were unusually apprehensive throughout the procedure. None of the patients described the headache as throbbing. The degree of headache bore no relation to the occurrence of previous headaches. Two patients who were subject to migraine headaches described the pain as similar to these headaches. In 1 case it was hemicranial, but not as severe as usual, and in the other it was bilateral and less severe.

Other Observations.—The onset of the headache in all but 2 instances occurred within from three to five seconds after injection of the air. These exceptions occurred in the 2 cases in which the greatest amounts of air were injected. One patient experienced headache sixteen seconds after 13 cc. of air was injected, and the other twenty-seven seconds after 16 cc. was introduced. Naturally, it took longer to inject the larger amounts of air.

The duration of the initial headache varied from five minutes to five hours. The duration was apparently unrelated to any other observation. Headaches that were made to disappear by shaking the patient's head always recurred, but in generalized form. Several persons subjected to withdrawal of fluid experienced typical postlumbar puncture headaches several hours after the procedure. The disorder for which the patients entered the hospital was related to the headache produced only in the 2 neurotic patients and the 2 patients with migraine headache.

COMMENT

The mechanism by which the bubbles of air produce a headache has not been revealed in these experiments. It is probable, however, that the pain is due to stimulation of the vascular or perivascular nerve endings along the greater vessels in the various cisterns and possibly in the roof of the third ventricle.

The indubitably sensitive areas are the cisternae magna, interpeduncularis (lower part), prechiasmatica and postchiasmatica and the body of the cisterna ambiens. In these cisterns there are to be found, respectively: the posterior spinal and posterior inferior cerebellar arteries; the upper end of the pontile artery, the origin of the superior

cerebellar and posterior cerebral arteries and the posterior communicating artery; the middle cerebral artery, the origin of the anterior cerebral artery and the anterior communicating artery, and the posterior cerebral artery and branches to the choroid plexus in the roof of the third ventricle. In addition, there are in these areas numerous smaller arteries and venous plexuses of various sizes. It has been shown at operation that stimulation of these vessels causes the type of pain which occurred in these experiments. The other areas less definitely determined to be sensitive foci are also characterized by large arterial channels. In the roof of the third ventricle lie the choroid plexus and its arteries; in the median frontal area is the anterior cerebral artery, and in the sylvian fissure, the middle cerebral artery.

Insensitivity of the lateral ventricles as shown in these experiments confirms surgical experience.[1c] It is possible that some of the other presumably sensitive areas are actually insensitive, for the following reason: Bubbles of air ascending from the cisterna magna and other basal cisterns may in transit have stimulated sensitive structures and passed on to lodge at higher levels, where they were eventually revealed by roentgenography. Such an occurrence would lend weight to the observations that the basal cisterns are in fact sensitive, but that the ventricles, and possibly certain hemispheric sulci, are in reality insensitive.

There were no significant changes in intracranial pressure. This implies that dural pressure, stretch or distortion was unlikely. In the presence of such small bubbles it is unlikely that much stretch of vascular elements occurred. Shaking, which would increase distortion, often relieved the headache. The onset of the response, in from three to five seconds, just allowed for the ascent of the air bubble from the lumbar to the basilar subarachnoid space. The irritant effect of the air is therefore probably mechanical or chemical. Stimulation must be mediated through the arachnoid or transmitted to periarterial neural extensions into the arachnoid, since the blood vessels in the cisterns are sheathed with arachnoid. (No air was seen outside the arachnoid or ventricular spaces.) Reception of the stimulus is probably by means of periarterial (or leptomeningeal) extensions of the periarterial nerve plexus along the larger cerebral arteries. The origin of these sensory nerves is as yet unknown. Central conduction of the impulses to the thalamus and higher centers may be along cranial nerves. Probably the fifth nerve predominates in any such pathway. These experiments yielded no information as to the central pathway. They have merely shown that a purely subarachnoid stimulus may cause headache in certain areas in the intact subject. Other sensitive and insensitive areas undoubtedly occur within the cranium.

This method of producing and localizing intracranial irritation promises to be useful in fields of investigation other than the study of headache, as, for example, in correlation of electroencephalographic studies.

SUMMARY AND CONCLUSIONS

A modification of the Elsberg and Southerland technic for the experimental production of headache in man is presented. The added refinements warrant further use of this method in the study of headache. The method has been applied in 20 subjects. Observations in this series justify the following conclusions:

A. It has been proved that: 1. Referred and localized headache may be produced in man by rapid introduction into the intact cranial subarachnoid and ventricular spaces of as little as 2 cc. of air.

2. Within limits of from 2 to 16 cc., the volume of air necessary to produce headache is an individual variant, unrelated to the location, degree or type of headache.

3. Alterations in intracranial cerebrospinal fluid pressure are not responsible for this type of headache. The initial headache caused by pneumoencephalography is not due to increased pressure within the third or any other ventricle, and the subsequent headache is not entirely due to increased pressure.

4. The cisternae magna, interpeduncularis, prechiasmatica and postchiasmatica and the body of the cisterna ambiens contain, or are bounded by, sensitive areas capable of producing referred headache on appropriate stimulation.

B. It is probable, but not proved, that: 1. The roof of the third ventricle, the median and lateral frontal areas and the sylvian fissure are also sensitive to such stimulation.

2. The walls of, and structures within, the lateral ventricles are insensitive to the irritant effect of air.

3. Pain from stimulation of the basal cisterns is referred forward to the frontal bones, orbits and deep orbital areas.

4. Lateralization and focal localization of pain are due, respectively, to homolateral and focal irritation of hemispheric meningeal areas.

C. It is suggested that this type of experimental headache and the earlier phases of headache accompanying pneumoencephalography are not due to distortion of dural areas or the meningeal vascular tree. This type of headache is probably due to direct (chemical or mechanical) stimulation of the sensory nerve endings along many of the larger branches of the internal carotid artery.

EFFECTS OF ETHYL ALCOHOL ON THE CEREBRAL CORTEX AND THE HYPOTHALAMUS OF THE CAT

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It is our purpose in this communication to report a series of experiments designed to investigate the effects of alcohol on the cerebral cortex and the hypothalamus of the cat, and to discuss briefly the significance of the results with regard to the functional interrelationships of these two portions of the central nervous system.

METHODS

The methods of physiologic and pharmacologic investigation developed in this laboratory have been described in previous reports;[1] as employed in the present study, they were as follows:

Acute Preparations (20 experiments).—The cat was anesthetized lightly with ether or pentobarbital sodium and prepared for kymographic recording of the respiration and blood pressure. By means of the Horsley-Clarke stereotaxic technic, insulated needle electrodes were then inserted into selected regions of the hypothalamus and cerebral cortex, rendering possible observation of the effects of stimulating these structures before and after various solutions of alcohol were injected directly into them or administered intravenously.

Recovery Preparations (15 animals; 49 experiments).—With the cat under anesthesia induced with pentobarbital sodium and with an aseptic technic, separate needle electrodes were inserted stereotaxically into the hypothalamus and posterior cruciate gyrus and then fixed firmly to the animal's calvarium. The next day the animal usually showed complete recovery from the operation and could be observed

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1. Masserman, J. H.: Effects of Sodium Amytal and Other Drugs on the Reactivity of the Hypothalamus of the Cat, Arch. Neurol. & Psychiat. **37**:617 (March) 1937; Destruction of the Hypothalamus in Cats, ibid. **39**:1250 (June) 1938; Action of Metrazol (Pentamethylenetetrazol) on the Hypothalamus of the Cat, ibid. **41**:504 (March) 1939; The Effect of Strychnine Sulphate on the Emotional Mimetic Functions of the Hypothalamus of the Cat, J. Pharmacol. & Exper. Therap. **64**:335 (Nov.) 1938. Masserman, J. H., and Haertig, E. W.: The Influence of Hypothalamic Stimulation on Intestinal Activity, J. Neurophysiol. **1**:350 (July) 1938. These reports also contain observations that were used as controls in the present study.

in a waking, mobile state for (*a*) the responses to faradic stimulation of the cortex or the hypothalamus, (*b*) the effects of injecting various concentrations of alcohol into these structures and (*c*) the changes produced in the electrical reactions by these injections or by the intravenous administration of alcohol. After the final experiment with each animal, serial sections of the brain were made in order to check microscopically the exact position of the electrodes.

RESULTS

Acute Experiments.—In 9 animals, the injection of 0.1 cc. of a 0.01 to 0.04 per cent concentration of alcohol in Locke's solution directly into one side of the hypothalamus caused no change in the effects of faradic stimulation of either side of this structure, other than that in 3 instances the pilomotor, unguimotor and skeletal muscular responses were slightly augmented for several minutes. However, when the concentration of the alcohol was increased to above 0.06 per cent there was a definite decrease in the respiratory, vasomotor and other hypothalamic reactions, especially when the stimulating current was confined to the region of injection by the use of a bipolar electrode (fig. 1). In 9 acute preparations used as controls, the responses to faradic stimulation of the hypothalamus were not affected materially either by the injection of 0.2 cc. of from 0.02 to 0.10 per cent alcohol in the cortex or thalamus or by the administration of from 4 to 12 cc. per kilogram of a 25 per cent solution of alcohol in physiologic solution of sodium chloride intravenously, although in 2 of the latter instances transient hypopnea and fall in blood pressure were observed (fig. 2).

Recovery Preparations.—Control Observations: As previously reported, faradic stimulation of the hypothalamus in unanesthetized animals produced a combination of vegetative and neuromuscular reactions suggestive of rage and fear: dilatation of the pupils; extrusion of the claws; erection of the hair; salivation; forced urination; baring and chopping of the teeth; lashing of the tail, and well coordinated crouching, sniffing, seeking, running and fighting movements. Stimulation of the posterior cruciate cortex produced a quite different set of responses: A faradic current of 2 to 4 volts induced alternate flexion and extension of the legs on the opposite side of the body, torsion of the trunk, rolling movements, and occasionally slight piloerection, cyclodilatation and licking or chewing motions; stronger cortical stimuli (4 to 12 volts, alternating current) caused increased vegetative responses accompanied by clonic muscular convulsions with jacksonian progression and persistence of a few seconds to fifteen minutes after cessation of the stimulus.

Direct Injections: Injection of 0.1 cc. of from 0.02 to 1.25 per cent alcohol into either the hypothalamus or the motor cortex did not produce discernible signs of pain or other spontaneous effects; however, the electrical reactions of the injected tissue were modified as follows:

(*a*) In 2 of 4 experiments, 0.02 per cent alcohol lowered the threshold of response to faradic stimulation in both the cortex and the hypothalamus by 0.5 to 1 volt.

(*b*) In 8 animals, 0.1 cc. of 0.04 per cent alcohol produced no consistent effects.

(*c*) In 9 animals, the direct injection of 0.1 cc. of higher concentrations of alcohol (up to 1.0 per cent) consistently raised the strength of current necessary for minimal and maximal reactions in both the cortex and the hypothalamus from 0.5 to 3 volts above the control levels.

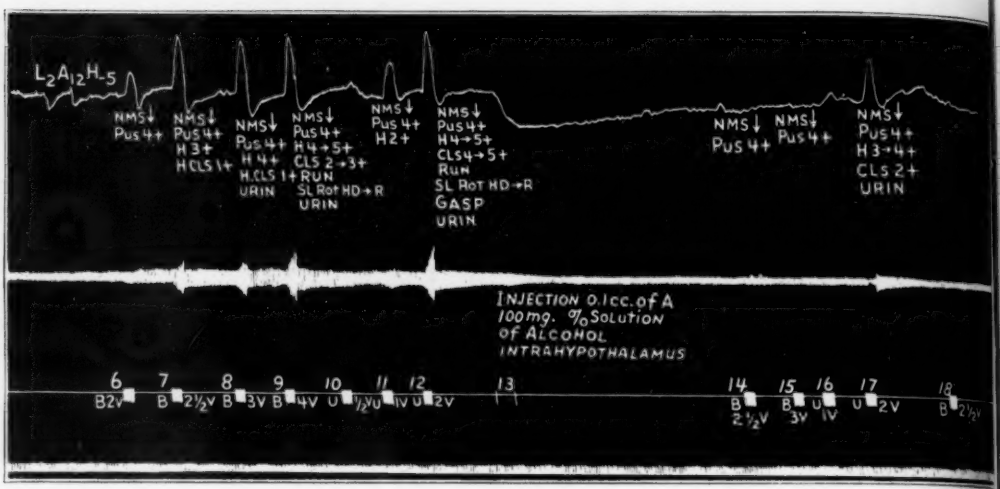

Fig. 1.—Effect of the injection of 0.1 per cent alcohol into the hypothalamus on its reactions to faradic stimulation. In this and in the following figure, the line tracings from above down represent, respectively, the blood pressure, the respiration, the signal record and the time, marked in seconds. The notation L_2 A_{12} H_{-5} indicates the stereotaxic setting of the needle electrode in the left anterior portion of the hypothalamus; other code markings are as follows: *Cls*, extrusion of the claws; *Gasp*, gasping respirations; *H*, erection of the hair; *Hd*, rotation of the head; *HL*, movements of the hindlegs; *NMs*, retraction of the nictitating membranes; *Pus*, dilatation of the pupils; *R*, right; *Rot*, rotation; *Run*, running movements; *Sl*, slight; *Urin*, urination; *0* to *5*, the scale of intensity of each of these responses. Each signal record is marked by the serial number of the stimulus above the line and by the strength of the current employed (0.5 to 4 volts) below; each stimulus is also labeled *B*, meaning bipolar stimulation with a faradic current limited to the tissue immediately about the tip of the electrode, or *U*, representing unipolar stimulation of a larger portion of the hypothalamus.

At signals *6*, *7*, *8* and *9* bipolar faradic stimuli increasing from 2 to 4 volts were applied to the left side of the hypothalamus, causing rises in blood pressure of from 8 to 70 mm. of mercury, transient hyperpnea and characteristic hypothalamic responses of increasing intensity, such as retraction of the nictitating membranes, dilatation of the pupils, erection of the hair, extrusion of the claws, urination, rotation of the head and running or pawing movements. At signals *10*, *11* and *12* unipolar stimuli were applied, eliciting with weaker currents the same responses from larger portions of the hypothalamus. At *13*, 0.1 cc. of 0.10 per cent alcohol in Locke's solution was injected directly into the hypothalamus through the needle electrode, causing a transient fall in blood pressure, but no other apparent effects. However, the subsequent responses of the hypothalamus to faradic stimulation (signals *14* to *18*) were found to be greatly diminished, especially when, by means of bipolar stimulation, the current was limited to the tissue into which the alcohol was directly injected.

(*d*) Injection at either site of 0.1 cc. of from 0.01 to 1.25 per cent alcohol did not noticeably modify the faradic reactions at the other.

It appeared, therefore, that whereas 0.02 per cent alcohol might have a slightly stimulating effect on nerve tissue, concentrations of alcohol above 0.06 per cent were locally depressant or toxic when injected into either the hypothalamus or the cerebral cortex.

Intravenous Injections: During the intravenous administration of from 4 to 12 cc. per kilogram of a 25 per cent solution of absolute alcohol in physiologic solution of sodium chloride, at the rate of 10 cc. per minute, the animal rapidly became quiet, and thereafter showed moderate hyperpnea, variable cyclodilatation and nystagmus, ataxia with muscular flaccidity, impairment of righting reflexes, partial analgesia, somnolence and, finally, apathetic stupor, which persisted for an hour or longer. That these effects were related to interference with cortical function was indicated by the consistent rise (from 1 to 12 volts) in the threshold of minimal and maximal responses to faradic stimulation of the cortex and by the fact that the animal relapsed into stupor almost immediately after the cortical

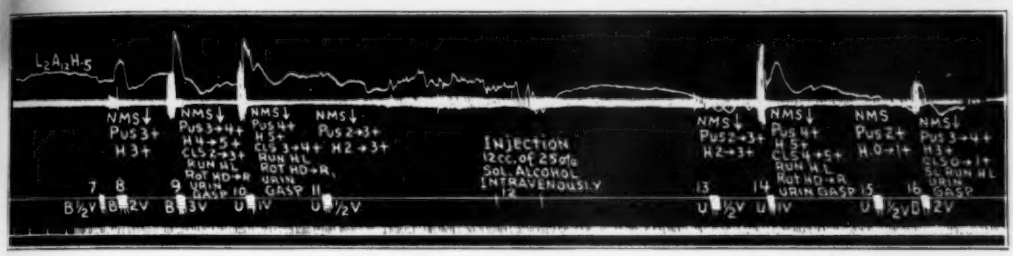

Fig. 2.—Effect of the intravenous injections of alcohol on the hypothalamus (notations as in fig. 1).

At signals *7* to *11* typical vegetative and motor responses to bipolar and unipolar stimulation of the hypothalamus are recorded. At *12,* 12 cc. of a 25 per cent solution of alcohol in physiologic solution of sodium chloride was injected intravenously; subsequent stimulation of the hypothalamus (signals *13* to *19*) showed either no significant changes in its reactivity or slight lowering in the threshold of response to bipolar stimuli.

stimulation was discontinued. However, the effects of the alcohol on the hypothalamus appeared to be different, in that (*a*) hypothalamic stimulation, even in an animal in alcoholic stupor, caused it to arouse itself to a state of comparative alertness and activity (despite the persistence of some motor ataxia) for periods of from one to ten minutes, and (*b*) in 6 of 10 animals the various pseudoaffective hypothalamic reactions, including vocalizations, vegetative responses and running and fighting movements, were obtained with currents from 1 to 3 volts less than those required before administration of the alcohol. The indications were, therefore, that whereas the intravenous administration of from 1 to 3 cc. per kilogram of absolute alcohol depressed the functions of the cortex, the reactions of the hypothalamus were either unaffected or actually increased in intensity.

COMMENT

Many previous animal experimental,[2] clinical[3] and pathologic[4] studies have indicated that alcohol has a depressant and toxic effect on the cerebral cortex, despite a concurrent accelerant influence on the cerebral blood flow.[5] However, the action of alcohol on lower centers, particularly those in the diencephalon, has not been directly investigated, although the drug has been shown to produce widespread pathologic changes not only in the cortex but also in the hypothalamus and other periventricular structures.[6] In our experiments the injection of alcohol in greater than 0.06 per cent concentration directly into the cortex or the hypothalamus caused diminution in the local electrical reactivity of

2. (*a*) Pilcher, J. D.: Alcohol and Caffeine: A Study of Antagonism and Synergism, J. Pharmacol. & Exper. Therap. **3**:267 (July) 1912. (*b*) Chauchard, A.; Chauchard, B., and Kajiwara, S.: Action de l'alcool sur l'excitabilité des neurones moteurs de l'écorce cérébrale, Compt. rend. Soc. de biol. **105**:778, 1930. (*c*) Lapicque, L., and Kajiwara, S.: Changements dans les chronaxies périphériques sous l'influence de l'alcool, ibid. **105**:632, 1930. (*d*) Dorsey, J. M., and Travis, L. E.: Effect of Alcohol on the Patellar Tendon Reflex Time in Dogs, Arch. Neurol. & Psychiat. **24**:48 (July) 1930. (*e*) Bernhard, C. G., and Goldberg, L.: Nystagmus spontane par suite d'intoxication aiguë par l'alcool, Acta med. Scandinav. **84**:36, 1934. (*f*) Gantt, W. H.: Effect of Alcohol on Cortical and Subcortical Activity Measured by the Conditioned Reflex Method, Bull. Johns Hopkins Hosp. **56**:61 (Feb.) 1935.

3. (*a*) Kraepelin, E.: Ueber die Beeinflussung einfacher psychischer Vorgänge durch einige Arzneimittel, Jena, H. Pohle, 1892. (*b*) McDougall, W.: On a New Method for the Study of Concurrent Mental Operations and Mental Fatigue, Brit. J. Psychol. **1**:442, 1905. (*c*) Travis, L. E., and Dorsey, J. M.: Effect of Alcohol on the Patellar Tendon Reflex Time, Arch. Neurol. & Psychiat. **21**:613 (March) 1929; (*d*) Patellar Tendon Reflex Time in Psychiatric and in Neurologic Cases, ibid. **22**:99 (July) 1929. (*e*) Moeren, M.: Zur Frage der motorischen Erregung unter Alkoholwirkung, Ztschr. f. d. ges. Neurol. u. Psychiat. **130**:160, 1930. (*f*) Dodge, R., and Benedict, F. S.: Psychological Effects of Alcohol, Publication 232, Carnegie Institution of Washington, 1932. (*g*) Malamud, W.; Lindemann, E., and Jasper, H.: Effect of Alcohol on the Chronaxia of the Motor System, Arch. Neurol. & Psychiat. **29**:790 (April) 1933. (*h*) Newman, H. W.: Alcohol Injected Intravenously: Some Psychological and Psychopathological Effects in Man, Am. J. Psychiat. **91**:1343 (May) 1935.

4. (*a*) Doi, M.: Ueber die Veränderung der Nervenzellen und Nervenzellensynapse bei Alkoholvergiftung, Mitt. ü. allg. Path. u. path. Anat. **7**:41 (Sept.) 1931. (*b*) Martland, H. S.: The Pathology of Acute and Chronic Alcoholism, in Alcohol and Man, New York, The Macmillan Company, 1932, chap. 9, pp. 201-223. (*c*) Bender, L., and Schilder, P.: Encephalopathia Alcoholica, Arch. Neurol. & Psychiat. **29**:99 (May) 1933.

5. Thomas, C. B.: Effect of Alcohol on Cerebral Vessels, Arch. Neurol. & Psychiat. **38**:321 (Aug.) 1937.

6. Bender, L.: Myelopathia Alcoholica Associated with Encephalopathia Alcoholica, Arch. Neurol. & Psychiat. **31**:310 (Feb.) 1934. Bender and Schilder.[4c]

both of these structures, but although alcohol has been shown to pass rapidly from the blood into the cells of the central nervous system,[7] the evidence from direct injections could not be considered physiologic because of the violation of the normal blood-encephalic barrier. Of more significance, therefore, is our finding that the intravenous administration of from 1 to 3 cc. per kilogram of absolute alcohol actually increased the reactivity of the hypothalamus while depressing both the motor and the vegetative[8] functions of the cortex. Obviously, this analeptic effect of alcohol on the hypothalamus does not necessarily mean that alcohol has a directly stimulant action on the structure, since the increased hypothalamic responses could also be accounted for by diminution in the normal inhibition of the hypothalamus by the cortex[9] during the alcoholic intoxication of the latter. Nevertheless, the obverse of this relationship—the influence of the hypothalamus on the cortex—is demonstrated in our experiments by the fact that localized faradic stimulation of the hypothalamus in the intoxicated animals not only induced the usual transient vegetative and motor emotional mimetic reactions, but also initiated the more complicated, maintained and directed defensive and offensive behavior in which, according to present concepts of the integration of central nervous activity,[10] the cortex necessarily participates. In contrast to the motor coordinating functions of the cortex, however, its temporal inhibitory influence on lower centers was apparently impaired in the intoxicated animals, permitting the emotional mimetic behavior to continue for longer periods than in the normal controls.

SUMMARY AND CONCLUSIONS

By means of original modifications of the Horsley-Clarke technic, the effects of the intravenous administration of various concentrations of alcohol on the hypothalamus and the cruciate cortex of the cat were studied in 35 animals. The results indicate that:

1. The direct injection of alcohol in strengths of from about 0.02 per cent may have a slightly stimulant effect on both the hypothalamus

7. Newman, H. W., and Mehrtens, H. S.: Alcohol Injected Intravenously: Penetration into the Cerebrospinal Fluid in Man, Arch. Neurol. & Psychiat. **30**: 1092 (Nov.) 1933. Harger, R. N., and Halpien, H. R.: Storage of Ethyl Alcohol, J. Biol. Chem. **120**:689 (Sept.) 1937.

8. Crouch, L., and Thompson, J. K.: Autonomic Functions of the Cerebral Cortex, J. Nerv. & Ment. Dis. **89**:328 (March) 1939.

9. Bard, P.: A Diencephalic Mechanism for the Expression of Rage, Am. J. Physiol. **84**:490 (April) 1938; The Central Representation of the Sympathetic System as Indicated by Certain Physiologic Observations, Arch. Neurol. & Psychiat. **22**:230 (Aug.) 1929.

10. Papez, J. W.: A Proposed Mechanism of Emotion, Arch. Neurol. & Psychiat. **38**:725 (Oct.) 1937.

and the cruciate cortex, although the findings are not determinative. However, alcohol injected in a concentration greater than 0.06 per cent is definitely toxic to tissues of the central nervous system.

2. The intravenous administration of absolute alcohol in a dose of from 1 to 3 cc. per kilogram has a depressant effect on the motor responses of the cortex to electrical stimulation, but in unanesthetized animals the emotional mimetic reactions of the hypothalamus are unaffected or are actually increased in intensity and duration.

3. There is support for the view that whereas the cortex has an inhibitory function on lower centers, the reverse relationship also holds true, in that the cortex is likewise under the influence of the hypothalamus and both structures are functionally interrelated in the neural mechanisms of emotional expression.

CHANGES IN THE ELECTROENCEPHALOGRAM DURING METRAZOL THERAPY

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We have recorded the electroencephalogram of a patient under treatment for schizophrenia, beginning before each injection of metrazol and continuing without interruption for from two to three hours. The patient was given 24 metrazol treatments. Reactions during 22 of his treatments were so recorded, and several subsequent studies were made for a year after termination of the treatment.

REPORT OF A CASE

History.—The patient was a man aged 33, the second oldest of five siblings, four living and one dead, in a family with no known history of mental disorder. There was no information concerning his birth. He was obese at the age of 10, but later became slender, with a tendency to be underweight. He had influenza in 1918. He took prizes for scholarship in high school, spent two years in graduate work and was one of a few students chosen to study in Europe in 1929. He had always worked hard; he worried about examinations in school. He was thorough, a leader among friends and pleasant. He was not thought to be of the daydreaming type, or to be individualistic or introspective.

In 1934, while in Europe, after being seclusive for about two months, he began to have ideas of persecution. A month later he was taken to a clinic. After five days of observation a diagnosis of "paranoid state, probably of schizophrenic origin" was made. Fever therapy with sulfur was undertaken for five weeks, with no psychic improvement. In March 1936 he was returned to the United States, with a poor prognosis, and was admitted at the McLean Hospital.

On admission he was seclusive and careless in dress, stared into space and turned his head as if having auditory hallucinations. He showed a good deal of motor activity, was excited and uncooperative, became assaultive and screamed, usually at night. There was no appreciable change in his condition from 1936 to 1938.

The patient was cooperative throughout the treatments, but at times was confused. He did not resist the metrazol, even though he resented it bitterly at times.

The electroencephalographic studies were aided by a grant from the Josiah Macy Jr. Foundation.

From the Department of Physiology of the Harvard Medical School, and the McLean Hospital, Waverley, Mass.

Read at the Sixty-Fifth Annual Meeting of the American Neurological Association, Atlantic City, N. J., June 7, 1939.

Electroencephalographic Procedure.—The apparatus used was a two channel, condenser-coupled, ink-writing oscillograph, built by A. M. Grass, of the Harvard Medical School. Broadly tuned electrical filters were put into the circuit for all control records for the purpose of measuring, by standard methods, the alpha and delta indexes, as carried out with normal persons at the Harvard Medical School.[1] The two channels were completely independent of one another, so that it was possible to record simultaneously from the occipital and the motor area of the brain by monopolar or by bipolar technic. Electrode placements were made 2 cm. above the inion and on the vertex in the midline. Reference electrodes were attached to the ear lobes and connected in parallel. The patient was settled comfortably, lying on a bed with eyes closed and muscularly relaxed and quiet, while a routine record was made. The electroencephalogram was begun before the injection of metrazol and was continued for about two hours during the treatment, until the pattern had returned to normal for thirty seconds. A sample of blood was taken ten minutes before the injection and ten minutes after the end of the convulsions. No significant changes in the blood chemistry were detected.

Convulsive Responses to Injections of Metrazol.—The normal occipital record for this patient had an alpha rhythm of from 10 to 12 waves per second (fig. 1), which appeared about 75 per cent of the time. The alpha rhythm[2] is defined as the rhythm, usually about 10 waves per second, most prominent at the occiput, which is reduced when the eyes are open and returns to full size when the eyes are closed again.

When a sample of blood was taken or metrazol injected, the patient would watch the needle entering his arm vein, so that, since his eyes were open, the normal percentage of alpha rhythm was reduced. Insertion of the needle did not otherwise modify the pattern. Muscle potentials, which were caused by the tension of the neck muscles as the patient raised his head from the pillow to watch the procedure, blurred the record to some extent.

Four separate stages following the injection of metrazol can be differentiated in the electroencephalographic records from both the occiput and the vertex.

Stage 1: The first change occurred from nine to thirty-five seconds after the end of the injection of metrazol. A burst of extremely high voltage waves appeared in the electroencephalogram simultaneously with a single violent twitch exhibited by the patient (line 3, fig. 1).

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1. (*a*) Davis, H., and Davis, P. A.: Action Potentials of the Brain in Normal Persons and in Normal States of Cortical Activity, Arch. Neurol. & Psychiat. **36:** 1214 (Dec.) 1936. (*b*) Davis, P. A., and Davis, H.: The Electroencephalograms of Psychotic Patients, Am. J. Psychiat. **95:**1006, 1939; unpublished data. (*c*) Hoagland, H.; Cameron, D. E., and Rubin, M. A.: The Electroencephalogram of Schizophrenics During Insulin Treatments: The "Delta Index" as a Clinical Measure, ibid. **94:**183, 1937.

Our technic differs from that described by Hoagland in that (1) our amplification is slightly greater and (2) we place in our electrical circuit a broadly tuned filter (peak at 3 cycles), which partially suppresses the alpha and faster waves. In measuring the excess length of line traced by the pen per meter of tape, we disregard all wavelengths shorter than twenty-five hundredths of a second. Otherwise, records such as lines 5 and 6 in figure 5 would show a higher "delta excess" than line 7, and we regard line 7 as more abnormal than lines 5 or 6. In general, the slower the delta waves, the greater is the abnormality.

2. (*a*) Berger, H.: Ueber das Elektrenkephalogramm des Menschen, Arch. f. Psychiat. **87:**527, 1929. (*b*) Davis and Davis.[1a]

Stage 2: After this burst of high voltage waves, the normal frequency of about 10 per second was seen to emerge and the voltage to increase in both areas for a period of seven to eighteen or twenty seconds (line 4, fig. 1). The rhythm did not speed up or change.

Stage 3: This normal frequency was gradually obliterated by the oncoming fast waves which were superimposed on the 10 per second waves, and which increased in voltage until they dominated the picture.

Stage 4: These fast waves, after they had obliterated the previous waves of normal frequency, began to form into groups which gradually spaced out to a slower and slower tempo, and eventually showed reduction in voltage until they abruptly stopped in the two areas simultaneously and the record became flat. The convulsion ended at this time.

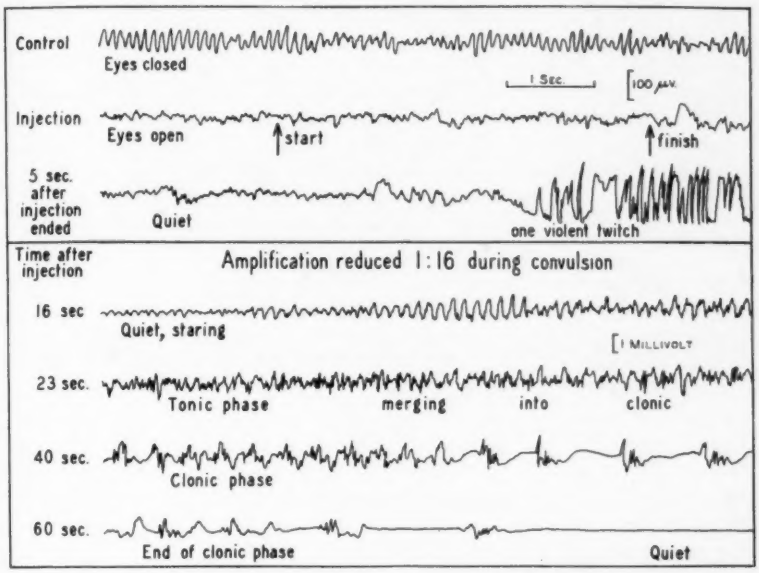

Fig. 1 (Feb. 15, 1938).—Electroencephalograms recorded before and during a convulsion produced by metrazol (from Davis and Davis [5]). Leads were taken from the occiput and the vertex in the midline. Upward deflection indicates that the occiput became electrically more negative in relation to the vertex. Note the great reduction of amplification which was necessary during the actual convulsion.

Line 1 is a normal control record; lines 2 and 3 represent stage 1; line 4, stage 2; line 5, stage 3, and lines 6 and 7, stage 4.

At the time of the burst of extremely high voltage waves, the patient twitched violently once. He was then quiet and waiting, apparently quite aware of his surroundings, his eyes resting on the physician. As generalized rigidity slowly crept over him, his muscles gradually became tense. As he grew increasingly tense, his eyes gradually assumed an unseeing expression. This was the tonic phase, which merged imperceptibly into the clonic phase of the convulsion. He had been conscious up to the time of the clonic phase. To test this, he was asked during some of the treatments to count from the end of the injection as long as he could, slowly and steadily. Once the patient counted to ten, slipping over eight and nine.

when a momentary lag occurred, his lips moving silently and eyes fluttering, then quietly whispering "ten." At the time he said "ten" the clonic phase was well established, and the extremely high voltage waves dominated the picture. After the treatment was over and the patient had returned to consciousness, he was asked how far he counted. He said he remembered counting to four, then "going out like a light."

The transition from the tonic to the clonic phase of the convulsion was gradual and could not be observed any more readily in the electroencephalogram than by watching the patient. In the postconvulsive state, crossed extension, Babinski and flexion reflexes and foot clonus could be elicited to a variable extent. The general lack of response was severe enough that artificial respiration often was given for five to fifteen seconds, to assure the patient of return to spontaneous breathing.

The postconvulsive period may be divided into five stages (fig. 2).

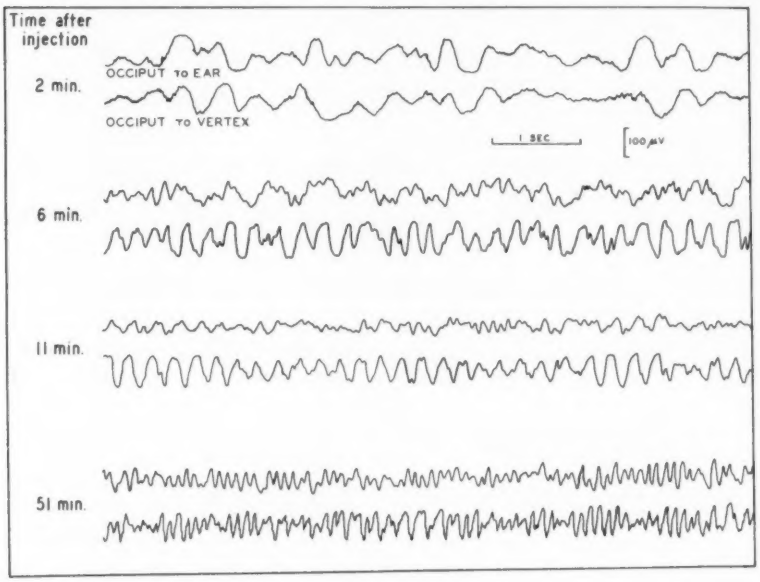

Fig. 2 (Feb. 15, 1938).—Four pairs of simultaneous electroencephalographic records (continued from figure 1) taken during recovery from a metrazol convulsion (from Davis and Davis [5]). Amplification is same as that in the first half of figure 1, before the convulsion. Postconvulsive stage 1 is not shown, since it is a transition from an almost flat line (fig. 1, line 7) to stage 2, represented in the first line.

The first pair of lines represents postconvulsive stage 2; the second pair, postconvulsive stage 3; the third pair, postconvulsive stage 4, and the fourth pair, postconvulsive stage 5.

Stage 1: After the end of the convulsion, the electrical pattern showed extremely slow, smooth, random waves of reduced voltage and followed closely the unconscious condition. After spontaneous respiration became reestablished, the voltage of this random delta activity, as it is called, slowly increased from about 30 to 150 or 200 microvolts.

Stage 2: The delta waves, one-half to two seconds in duration, appeared in the motor and the occipital area simultaneously. These areas of the brain seemed to be depressed in the same way. At no time during this stage did the patient respond to questions or noises. Random behavior, such as groaning or rolling about, turning the head or waving the arms sluggishly, occurred. The slow, random electrical activity continued for from one to several minutes.

Stage 3: The slow activity merged gradually into a faster delta activity in both areas. There appeared to be a progressive differentiation of the electrical activity in the two areas, which became more and more independent of each other. It appeared that the brain was recovering from a generalized physiologic depression.

Stage 4: In the occiput, the faster delta activity shifted to waves of 10 per second frequency, which came in sporadically at first, then intermittently, until they began to assume the normal pattern. In the motor area, the faster delta activity continued for only a short time, and was soon replaced by 100 microvolt, 4 to 5 per second waves, which continued steadily and usually without other superimposing frequencies for from ten minutes to half an hour. Eventually other frequencies broke into the continuous trains of 4 and 5 per second waves for short intervals. After the treatment, it was not always clear whether or not the alternation of the abnormal 4 and 5 per second waves and normal activity at the vertex was decreasing. Even when the normal pattern was maintained for thirty seconds, which was the criterion for ending the record, it was obvious that the episodes of 4 and 5 per second waves were still frequent.

Stage 5: The beginning of this stage was set arbitrarily as the first period in which there was normal activity in the two areas at the same time for thirty seconds or more.

In stage 3, the stage of transition from generalized delta activity to one in which frequencies could be counted, the patient responded to questions by turning to the physician, fixing his gaze, then answering when his name was called. One obtained the impression that he was aware of what was going on about him even before he responded. In a similar condition, a normal person, awaking from sleep, can be aware of what is going on about him, yet be quite unresponsive or responsive only in a retarded manner. As the patient's electroencephalogram returned to normal the state of consciousness became progressively clearer and similar to the slow awakening from a dream or deeper sleep. The foregoing description is in agreement with the accounts already given by Cook and Walter,[3] Strauss and Rahm,[4] Davis and Davis[5] and Rubin and Wall.[5a]

The patient was not mentally confused between the treatments which ended in convulsions. The nurses' reports gave excellent accounts of the patient's overt behavior in the ward, and conferences with a physician (W. S.) revealed that all his mental abnormalities, such as his paranoid ideas, auditory hallucinations, poor orientation and lack of insight, were still present, though fairly well repressed.

The accompanying table does not show any significant correlation between the speed of injection and amount of metrazol and the effect or its duration. How-

3. Cook, L. C., and Walter, W. G.: The Electroencephalogram in Convulsions Induced by Cardiazol, J. Neurol. & Psychiat. **1**:180, 1938.

4. Strauss, H., and Rahm, W. E., Jr.: Reactions of the Electroencephalogram to Metrazol Injections, Proc. Soc. Exper. Biol. & Med. **40**:1, 1939.

5. Davis, H., and Davis, P. A.: The Electrical Activity of the Brain: Its Relation to Physiological States and to States of Impaired Consciousness, A. Research Nerv. & Ment. Dis., Proc. **19**:50, 1939.

5a. Rubin, M. A., and Wall, C.: Brain Potential Changes in Man Induced by Metrazol, J. Neurol. & Psychiat. **2**:107, 1939.

ever, it is well recognized that the more rapid the injection the more likely a convulsion is to occur.

Convulsions following metrazol injections have been called "grand mal" epilepsy. Although in the electroencephalogram the clonic phase appears to resemble the clonic phase of grand mal epilepsy,[6] the onset of and recovery from metrazol convulsions are quite different.

A motion picture was taken of this patient during one of his treatments. A control record preceded the injection. The floodlights were then turned on while the electroencephalogram was continued. Suddenly, the normal occipital record was replaced by an extraordinary episode (fig. 3), which did not extend to the

Clinical Effect and Duration of Stages in the Electroencephalogram During Metrazol Treatments

						Electroencephalogram			
Date, 1938	Electro-encepha-alo-gram No.	Metra-zol in 10% Solu-tion, Gm.	Injec-tion Time, Sec.	Type of Response	Duration of Response, Sec.	End of Injection to First Twitch: Stage 1 (Sec.)	First Twitch to Clonic Phase: Stage 2 (Sec.)	Clonic to Flat Phase: Stage 3 (Sec.)	First Twitch to Flat Phase: Stages 1-3 (Sec.)
1/29	..	0.4	...	Convulsive					
1/31	..	0.4	...	Convulsive					
2/ 2	1	0.4	...	Convulsive	60	....	19	37	56
2/ 4	2	0.4	9.7	Convulsive	42	15	7	27	34
2/ 7	3	0.4	5.7	Convulsive	55	15.7	13	38	51
2/ 9	4	0.4	2.3	Nonconvulsive	90-120	19			
2/11	5	0.5	3.3-6?	Nonconvulsive	..	9.3-12?			
2/12	6	0.7	3.3	Convulsive	47	11	13	32	45
2/15	7	0.7	4.3	Convulsive	46	10.7	11	46	57
2/18	8	0.7	6.3	Convulsive	48	11.3	15	32	47
2/23	9	0.7	10	Convulsive	51	35	15	32	47
2/26	10	0.7	9.7	Nonconvulsive	..	No twitch			
2/28	11	0.7	2.3	Convulsive	65	9.7	9	47	56
3/ 3	12	0.7	4	Convulsive	68	11	14	37	51
3/ 8	13	0.7	3.3	Convulsive	57	8.7	13	40	53
3/11	14	0.7	3.7	Convulsive	67	9.7	15	40	55
3/15	15	0.7	3.3	Convulsive	52	10	14	44	58
3/17	16	0.7	2	Convulsive	55	10	13	47	60
3/19	17	0.7	4	Nonconvulsive	120±	No twitch			
3/20	18	0.7	2.7	Convulsive	..	9	14	32	46
3/22	19	0.7	3.7	Convulsive	53	9.3	13	49	62
3/24	20	0.7	3.3	Convulsive	66	10.3	14	48	62
3/26	21	0.7	3.3	Convulsive	53	17.3	10	31	41
3/29	22	0.7	3.3	Convulsive	53	10.3	11	40	51
4/ 7	23	...	...	.....	..		Follow-Up		

motor area. We believe that this unexpected reaction to sensory stimulation is definite evidence that the brain of this patient was in a highly sensitive and irritable condition, even though he had not had metrazol for two days. This reaction corresponds almost exactly to those obtanied by Gozzano in experiments on animals.[7]

6. Gibbs, F. A.; Davis, H., and Lennox, W. G.: The Electroencephalogram in Epilepsy in Conditions of Impaired Consciousness, Arch. Neurol. & Psychiat. **34**:1133 (Dec.) 1935. Gibbs, F. A.; Lennox, W. G., and Gibbs, E. L.: The Electro-Encephalogram in Diagnosis and in Localization of Epileptic Seizures, ibid. **36**:1225 (Dec.) 1936.

7. Gozzano, M.: Bioelektrische Erscheinungen bei der Reflexepilepsie, J. f. Psychol. u. Neurol. **47**:24, 1936. Fischer, M. H., and Löwenbach, H.: Aktionsströme des Zentralnervensystems unter der Einwirkung von Krampfgiften: II. Arch. f. exper. Path. u. Pharmakol. **174**:502, 1934.

He gave the animals mild doses of strychnine, and then applied strong stimuli such as bright lights and loud sounds and produced in the corresponding sensory areas of the cortex electrical outbursts which were like the patterns of larval grand mal seizures, and which sometimes spread and developed into generalized convulsions.

Nonconvulsive Responses to Injections of Metrazol.—Four times during the series of 24 treatments of this patient, varying amounts and speeds of injection of metrazol failed to produce convulsions. Samples of records giving both the common features and the variations of the nonconvulsive responses to metrazol are given in figure 4. Occipital records are not presented, since this area of the brain remained practically unaffected throughout. The motor area (vertex) revealed one feature common to all four records, namely, the characteristic abnormal positive waves appearing at irregular intervals. There were transient variations in response immediately after the injection which suggest larval or abortive convulsive effects. In one instance there was a twitch (line 1); in the next, a group of 6 or 7 per second waves, while in the last two records the positive waves were the main features of the response throughout. These nonconvulsive responses have been called "petit mal" and "psychic equivalents," but the electroencephalogram is distinctly different from the electroencephalographic record in epilepsy.[6]

In contrast to the clear mental state which he regained after each convulsion and maintained until the next treatment, the patient showed a distinctly different reaction, which persisted until the next treatment. He was less clear mentally, appeared to have more frequent hallucinations and was confused and less amenable to routine in the ward, even though he did not lose consciousness after the nonconvulsive treatments. After the first of the nonconvulsive responses on Feb. 9, 1938, he relapsed into his previous psychotic behavior. He had long staring spells and showed general withdrawal from the environment. After the second nonconvulsive treatment, on February 11, he alternated between psychotic and nonpsychotic behavior, was talkative and thought that he was the king of Spain. On February 26 he was talkative, puzzled about the purpose of the treatments, unable to relax and disoriented concerning persons and surroundings. On March 19 he was distracted, unable to concentrate and confused, and appeared to be having hallucinations.

The patient regressed considerably on February 26, and the clinical notes on February 28 stated that he "was more elated and talkative, and his auditory hallucinations troubled him more than for some time."

Evaluation of the Series of Control Electroencephalograms Taken Before Injections.—Measurements of the alpha index [8] and "delta excess" [9] and general descriptive evaluations of the control records were made by one of us at the Harvard Medical School, six months after the termination of treatments and in ignorance of the clinical data. The results of the evaluation are as follows:

The alpha index, or "per cent time alpha," remained throughout within the normal limits [10] of 10 per cent on either side of the mean (74 per cent in this patient), except in four measurements. These four exceptions did not correlate with the convulsive or nonconvulsive responses to metrazol or the degree of abnormality of the electroencephalogram.

The delta excess fluctuated widely, but within limits found in our normal series.

Slight abnormalities began to intrude into the control pattern soon after the course of metrazol treatments was begun.

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8. Davis and Davis.[1a] Davis and Davis.[1b]

9. Hoagland, Cameron and Rubin.[1c]

10. Davis and Davis.[1a] Davis, H.: The Electroencephalogram, Tabulae biol. **16**:116, 1938. Rubin, M. A.: A Variability Study of the Normal and Schizophrenic Occipital Alpha Rhythm, J. Psychol. **6**:325, 1938.

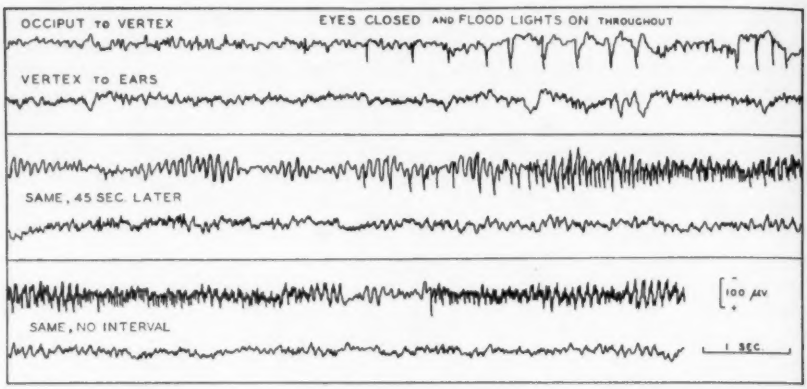

Fig. 3 (March 3, 1938).—Electroencephalogram taken as a control before injection of metrazol. The three pairs of simultaneous records show irritative response of the occipital area to stimulation by intense light. The vertex (motor area) remains unaffected by this stimulation, to which the visual area responds.

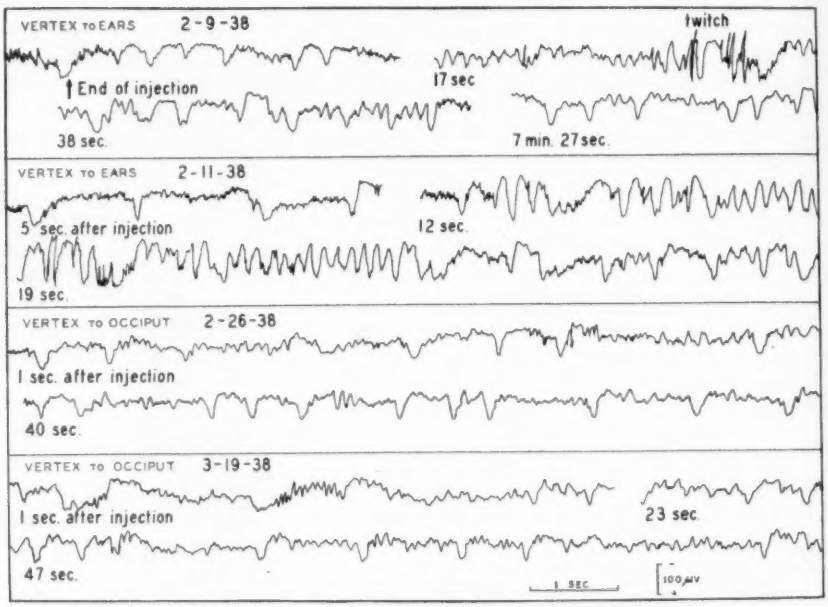

Fig. 4.—Samples of electroencephalographic records from four nonconvulsive responses to metrazol. Leads were from the vertex to one ear in each case. Downward deflection indicates that the vertex became electrically more positive in relation to the occiput.

The patient had 20 convulsions in the series of 24 treatments. Each subsequent control record taken before the next treatment showed that the normal alpha rhythm had returned. From the ninth record (February 23), however, each successive control record revealed an increasing number of abnormal episodes breaking into the alpha rhythm. From this time, the abnormalities progressed steadily to the end of the series, and were even more marked in the first follow-up record, taken nine days after treatment was over (line 7, fig. 5).

Four treatments produced nonconvulsive responses. The subsequent control records showed continuous abnormality.

Follow-Up Observations of the Patient for One Year: Electroencephalographic and Clinical Progress.—A follow-up electroencephalogram was taken nine days

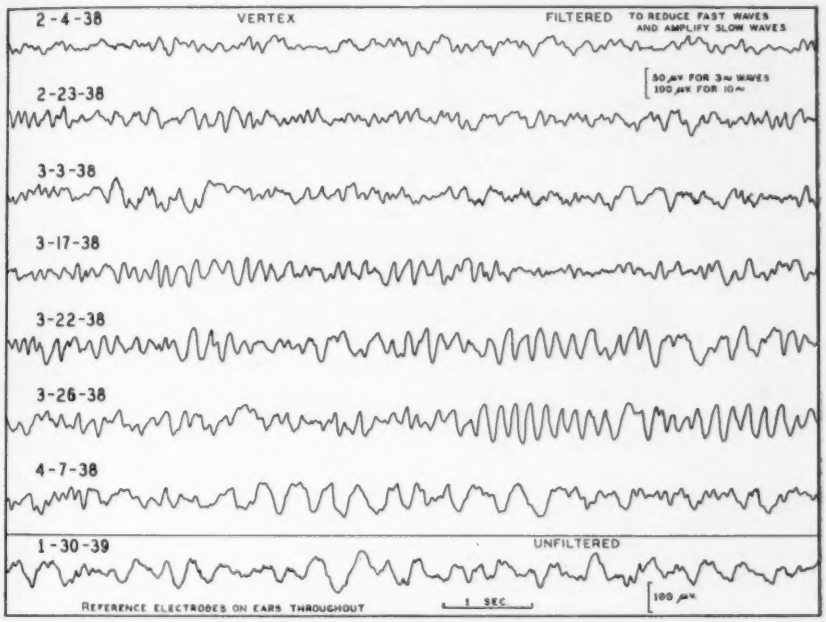

Fig. 5.—Samples from control electroencephalograms taken before metrazol treatments, showing increasing abnormality during and after the course of therapy. Lines 7 and 8 are records taken after termination of the course of therapy. The first seven records are taken with an electrical filter broadly tuned for the 3 per second frequency. The last record (1/30/39) was taken by standard technic without filter. If the filter and increased amplification had been used, as for the seven other records, the slow waves in the bottom line would have gone beyond the limits of the recording apparatus.

after termination of the metrazol treatments. Within six days of the last treatment the patient had regressed so rapidly to the acutely disturbed behavior shown before treatment began that he had to be returned to the ward for disturbed patients. Although the patient was sociable and cooperative when in the electroencephalographic laboratory, he appeared to be having hallucinations. He had short periods of mental clearness, in which he responded intelligently to questions and was perfectly aware of his surroundings. Every clinically observed hallucination coincided

directly with characteristic alterations in the electroencephalogram (fig. 6). But also at times when there were no clinical manifestations of any hallucinatory experiences alterations occurred. This may indicate that hallucinations were present, but since they were not expressed in any way they could not be recorded clinically.

For five months following the termination of metrazol therapy the patient remained clinically worse. He continued to be acutely disturbed, confused and disoriented as to time, place and persons, appeared to be having hallucinations and was assaultive. He lost the weight which he had gained during stimulation with metrazol.

Insulin treatment, initiated at the McLean Hospital by Dr. Manfred Sakel, was then begun and carried through by Dr. Lucy Jessner, of the McLean Hospital staff. The patient improved to a slightly higher level than was obtained with metrazol and the effect lasted longer. An electroencephalogram taken during the period of improvement with insulin therapy was as abnormal as the one taken at the end of the

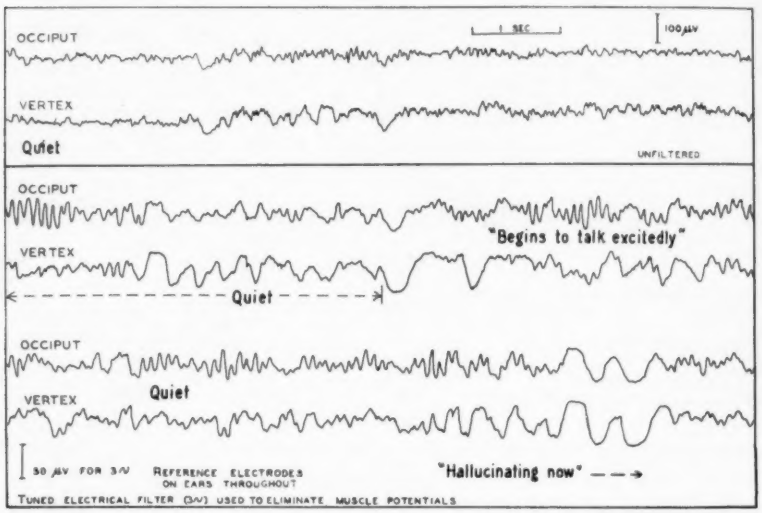

Fig. 6.—Electroencephalograms taken April 7, 1939, nine days after termination of the course of metrazol treatment (from Davis and Davis[5]). Three pairs of simultaneous records were taken from the occiput and vertex. Notations, such as "quiet" and "hallucinating," were made on the original record at the time. See text for details. The two lower pairs of tracings were recorded through a tuned electrical filter (3 per second), which reduces fast frequencies and quick waves, such as muscle potentials. The slow waves were amplified twice as much as by the standard technic.

metrazol treatment. A complete relapse followed termination of the insulin treatment. A month later another electroencephalogram was taken; the record showed a striking increase in abnormality (last line, fig. 5). This record was taken just a year and a day after the beginning of the first pharmacologic treatment at McLean Hospital.

It is unfortunate that a control record was not made before the metrazol therapy was started. After the second injection, the patient's clinical behavior had undergone a dramatic change from extreme psychosis to sudden clearing of the mental state. The electroencephalogram remained fairly normal during most of the

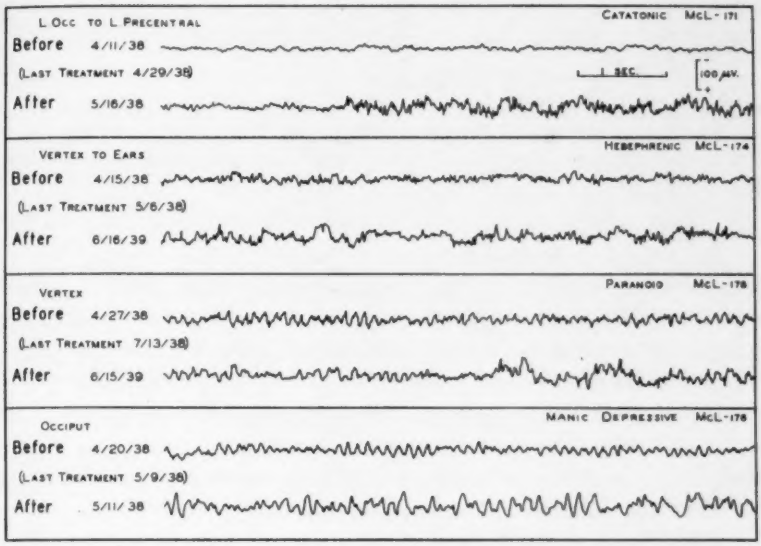

Fig. 7.—Electroencephalograms of 4 patients taken before and after a course of metrazol treatments, showing increase of abnormalities in each case.

McL-171, a man aged 31, hospitalized for seven years, received 6 convulsive and 3 nonconvulsive treatments. His behavior during shock was atypical, and he showed no clinical improvement. The routine electroencephalogram before treatment was definitely, but not greatly, abnormal, and afterward showed numerous bursts of irregular fast and slow waves, as seen in the figure. A complete electroencephalographic study led to the discovery, confirmed by a ventriculogram, of a large, inoperable porencephalic defect in the right occipital lobe.

McL-174, a man aged 39, hospitalized eight years, received 5 convulsive treatments, without clinical improvement. Treatment was discontinued because of psychic excitement and threatened circulatory collapse. The abnormalities which were present in his original record were greatly increased after the treatment.

McL-178, a woman aged 42, hospitalized six years, received 19 convulsive treatments in the last 3 of which camphor tetrazol was employed with no clinical improvement. The electroencephalogram was fairly normal before treatment, but afterward showed numerous irregularities and many abnormal episodes of both fast and slow waves of considerable voltage.

McL-176, a woman aged 41, with manic-depressive psychosis, hospitalized for a year and a half, received 9 convulsive treatments before the control record of May 11, 1938 was taken and 17 treatments subsequently. She showed partial temporary improvement clinically, but relapsed during the latter part of the treatment. The record before treatment was normal, but on May 11 it was clearly abnormal.

Two other patients had highly abnormal records (not shown in the figure) after a course of treatment, but adequate control records were not obtained before treatment.

progressive improvement, but abnormalities in the control records, appearing while the patient was maintaining his improvement, anticipated the clinical relapse which occurred shortly afterward with the development of more abnormalities in the electroencephalogram.

COMMENT

The basis of metrazol therapy is empiric. Statistics as to the success of the treatment in general are conflicting, owing at least in part to the varying criteria of what is meant by "improvement" or "social remission," terms which are inadequately defined and used differently.

This patient improved temporarily in his behavior during the first part of the metrazol treatment. From then on, however, the improvement ceased, and the electroencephalograms became increasingly abnormal. The abnormality of the electroencephalogram, nevertheless, may possibly be consistent with clinical improvement; for example, lesions of the frontal lobe have been reported to alleviate undesirable symptoms.

It is possible that metrazol may not damage all brains, particularly if the course of treatment is briefer, but 4 other patients (fig. 7), having from 6 to 26 treatments, all showed increased abnormality in the electroencephalograms. In the case of 2 other patients whose records were not taken, metrazol was discontinued after two or three treatments because of unfavorable reactions to the injections. Only 1 patient (with manic-depressive psychosis) in the entire group which received metrazol treatment has maintained improvement to date.

In our experience the clinical results of nonconvulsive responses were distinctly unfavorable. We have no explanation for the transient clinical improvement following a convulsion or for the confusion following nonconvulsive responses.

The variations between normal and abnormal patterns in the electroencephalogram are not immediately correlated with the clinical changes. The progressive increase in abnormality which was seen in the electroencephalograms as the metrazol treatments followed one another preceded the relapse chronologically.

SUMMARY

A man aged 33 years, who had been ill with schizophrenia for six years, was given 24 metrazol treatments, in which 20 convulsions were produced. An intensive electroencephalographic study was made during and after the course of treatments, with continuous recording throughout each treatment.

Four stages of electrical activity of the brain during the convulsions and five stages following the convulsions are described (figs. 1 and 2), as well as the associated clinical changes in the patient's behavior. After convulsive responses to metrazol the patient invariably exhibited a clear mental state as the electroencephalogram returned to normal.

The electroencephalograms taken during the onset of a metrazol convulsion and the postconvulsive recovery were unlike those obtained in epilepsy. There was a similarity to the electroencephalogram taken during the clonic phase of an epileptic convulsion.

The nonconvulsive response of the patient, in which he was confused and disoriented, revealed in the electroencephalogram a characteristic abnormal pattern and wave formation quite unlike the typical electrical pattern of petit mal epilepsy. This pattern was not seen after a convulsive response.

Unusual changes in the occipital electroencephalogram were observed when the eyes were stimulated by intense light. This indicated that the brain tissue was in a highly irritable condition (fig. 3).

After the treatment was terminated the patient had alternate periods of hallucination and a clear mental state. Changes in the electroencephalogram coincided directly with the hallucinatory manifestations (fig. 6).

With successive treatments a point was reached (after the eleventh injection) at which the normal physiologic functions of the brain tissue as represented in the electroencephalogram appeared to be definitely impaired. Impairment then increased in degree with further treatments (fig. 5).

The patient improved temporarily, but did not maintain his early improvement; he began to regress during the latter part of the treatment. Six days after the last treatment, he had regressed to his original condition.

A year later the damage or impairment of cerebral function as recorded by the electroencephalogram remained.

Mrs. Eleanore Snodgrass gave technical assistance; Dr. Hallowell Davis assembled the figures and, with the staff of the McLean Hospital, rendered constructive criticism of the manuscript, and Mrs. Jeannette Leighton made many excellent suggestions in its preparation.

DISCUSSION

DR. FREDERICK A. GIBBS: This paper has two very interesting aspects. It is a study of the effects of a convulsive drug given repeatedly over a number of days. It is a study of a drug which modifies the clinical condition of schizophrenic patients. Thus, the drug itself and this study bridge the borderland between epilepsy and schizophrenia. In epilepsy there are spontaneous variations in severity. Careful checking of the electrical record against these changes in the patient's condition has been exceedingly helpful in finding out the significance of the particular abnormalities that appear in epilepsy.

Every one who has studied schizophrenic patients has found it a source of great difficulty that there are no such rapid changes in the patient's condition to be correlated with changes in the electroencephalogram. With the use of metrazol and insulin shock therapy, however, there is the possibility that changes in the patient's condition and in the electrical record may be associated.

The authors are to be congratulated on having worked on both aspects of the subject so intensively; I hope they will continue and will report whether there

are variations from case to case and whether, if they can get a better therapeutic result, they can see more definite changes in the electroencephalogram, changes which can be correlated with the improvement.

Perhaps one should not be too pessimistic about the abnormalities that appear in the record after the use of metrazol. It is conceivable that abnormalities of this type may be necessary in order to counteract the abnormality with which one is dealing in schizophrenia. This is just speculation, but is it not possible that by damaging the brain one slows the abnormally fast activity which may be characteristic of schizophrenia? It has been seen in grand mal epilepsy, for instance, that at times the electrical activity of the cortex is too fast. The best anticonvulsants are drugs which when used in sufficient doses slow cortical activity. If one is dealing with some abnormal acceleration of cortical activity in schizophrenia it is entirely conceivable that really serious damage, sufficient to produce deceleration, would be effective therapy.

Dr. C. Macfie Campbell: This paper is, I think, a pioneer paper which will be followed by material which will perhaps enable one to arrive at more or less definite conclusions. Dr. Gibbs refers to the fact that those who are dealing with schizophrenia are worried at the absence of strict correlation between the clinical phenomena and the brain waves. What worries me, Dr. Gibbs, is not so much the absence of strict correlation, as the danger of premature correlation of brain waves with the extraordinarily complicated behavior which is called schizophrenia. The term "schizophrenia" has been utilized as if it had a rather specific significance, as if one were dealing with persons presenting a clinical picture or a syndrome with regard to which most neurologists are agreed. Whereas, schizophrenic patients form an extraordinarily complicated group, both in regard to the clinical picture and the outcome, and perhaps the etiology. The term may include various groups of disorders. Perhaps this new delicate technic may be a valuable agent in bringing a little order into the varied groups which have been brought together under this single term. However, the presentation here under discussion is that of an individual case which has been followed with the greatest care over a long period, and I think it is of the greatest value.

I have had the opportunity of going over a certain number of electroencephalograms of schizophrenic patients with Dr. Knox Finley; some of the patients had been treated with metrazol. Whether through timidity or prudence, we have never given a series of more than nine convulsions to our patients. We have found that at the end of treatment the waves seem to be much the same as before the treatment was started. I do not know whether, if there had been a longer previous record of this patient's electroencephalograms, they would always have presented the same type as during the first twenty minutes of observation. The future of this patient will deserve a later report. Certainly many patients who clinically appear beyond hope come back to their previous health and may resume their occupations. The brain waves in such cases have to be studied.

I am rather startled to hear in the present case that the brain waves change when hallucinations appear and also to find that it is assumed on the basis of the brain waves that hallucinations occurred but were not mentioned by the patient.

When patients are judged to be epileptic without convulsions, on account of their brain waves, or as schizophrenic and having hallucinations, which are perhaps subconscious, on account of their brain waves, one enters a very complicated territory. The clinical worker must feel grateful to those working with delicate instruments of precision in this important field.

Dr. Stanley Cobb: This work adds one more piece of evidence to show that metrazol actually injures the brain. There is clinical and histologic evidence, as well as roentgen evidence, of injury of the spine, and now there is electrical evidence indicating injury of the brain. This is interesting and important work. I should like to express my own opinion. I think that neurologists as physicians and as members of the American Neurological Association ought to wake up now to the fact that this is not real therapy. I think anything that actually injures the patients whom neurologists are supposed to be looking after should be stopped. The use of metrazol is the use of a perfectly dreadful drug.

MRS. P. A. DAVIS: In answer to Dr. Gibbs's remarks I should say that this patient was chosen because he did not have the frequency range mentioned in Dr. Gibbs's group of schizophrenic patients. He was chosen because his pattern was such a perfectly normal one, as far as any of us could see, and ran a 10 a second rhythm 74 per cent of the time. That particular rhythm stayed right through all of the patient's period of treatment until it was broken into by more and more slow waves, which we believe is perhaps evidence of damage.

If there is a fast frequency, I would agree that in slowing down the epileptic patients' fast waves one may make them more comfortable; and if one has a schizophrenic patient with fast frequencies, which one often does, one whose records are indistinguishable from those of epileptic patients, damage to the brain to some extent might slow down the fast waves and perhaps make him more amenable to the ward discipline and routine, and possibly get him out of the hospital. I did not follow those patients throughout their courses of treatments. It is too difficult to study the effects of treatment on more than one person at a time.

We are waiting for the successful case. If a physician can pick out a patient and say, "This patient is going to respond to metrazol or insulin and improve," we should like very much to follow him quite as intensively.

In answer to Dr. Campbell's remarks, I do not think it is necessarily a question of the number of doses. We had three patients who had less than five doses of 4 cc. of metrazol. The administration of the drug to one of them was stopped after the first dose because she went into circulatory collapse. Another patient, who did have eight treatments, had a record totally unlike this one. It was what we call a "choppy" record. He had a left-sided convulsion in the first treatment. Observing that this patient's head was badly misshapen, I begged to have a thorough neurologic check-up. They continued giving him eight convulsions, with rather bad results and long periods of asphyxia—over a minute. This patient was a physician who had been ill for six years. His family history was absolutely negative for schizophrenia, and he had 8 sisters and brothers who had no history whatever of mental disease. An extensive inquiry revealed that he had a porencephalic cyst in the right occipital lobe, apparently from an injury when he was 7 months of age. The remarkable thing was that he grew up and was able to go through college and medical school; he led a quiet, rather solitary life throughout. Following his case throughout as thoroughly as we did, we observed that the response to metrazol was every time totally different from the responses seen in all the other patients who had normal records from the start. I believed from the beginning that his brain must be pathologic, and this was confirmed by pneumoencephalograms and roentgenograms of the skull.

The hallucinations were beautifully correlated with changes in the electroencephalograms in this case. I do not want to give the impression, however, that the pattern seen in this case is characteristic of every hallucination. One gets all kinds of patterns with hallucinations. In our mescaline drug experiments the subject had hallucinations, and the pattern was totally unlike that seen in this man when he was hallucinating. However, when the consciousness is impaired physiologically in any way, the electroencephalogram does change. This finding has been consistent in all the work we have done in five years.

In answer to Dr. Cobb's remarks, I at first thought metrazol was excellent when I saw this man coming out of his fog of two or three years' duration and being quite clear for a day in between, but at the end of the treatment his regression was so rapid that I do not feel quite so happy about the metrazol experiments as I did last year. The patient has continued in his regression since, and it has lasted now for nearly one and one-half years.

Case Reports

POSSIBLE ETIOLOGIC ROLE OF ARSENIC IN DISTURBANCES OF THE CENTRAL NERVOUS SYSTEM ATTRIBUTED TO AVITAMINOSIS, WITH SPECIAL REFERENCE TO PELLAGRA

Report of a Case with Autopsy

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AND
ERNEST E. AEGERTER, M.D.
Instructor in Pathology
PHILADELPHIA

The following case is reported because it suggests that symptoms and pathologic changes identical with those found in pellagra and vitamin B complex deficiency may be directly or indirectly caused by arsenic.

REPORT OF CASE

A man aged 56 was admitted to the service of Dr. Temple Fay in the Temple University Hospital on April 18, 1938, with the complaint of progressive weakness, numbness and tingling of all extremities, marked ataxia of his hands and feet and a "bandlike" feeling about the abdomen. He dated the onset of the illness to seven months before admission, when he had "bronchitis" and a "cold in his nose," associated with tingling and numbness of his extremities.

Twenty-three years previous to the present admission (1915) gastroenterostomy had been done for a duodenal ulcer. The patient smoked as many as ten cigars a day and for many years had been a heavy drinker of whisky (as much as 1 quart [2 liters] every day). For one year previous to admission he had been troubled with digestive disturbances; appetite was poor, and the diet was limited, being deficient in fresh vegetables, fruits and dairy products.

Examination.—The patient was depressed and often cried. The complexion was sallow, and the skin on the trunk was thick and rough. There were slight brownish pigmentation of the hands and atrophy and thinning of the skin of the fingers. The finger nails were brittle and showed transverse white bands.

The pupils were normal. The eyegrounds and cranial nerves were normal. The deep tendon reflexes were absent, except in the left upper extremity, where the biceps and triceps responses were present but hypoactive. The Hoffmann and Babinski signs were not present.

Read at a meeting of the Philadelphia Neurological Society, Feb. 24, 1939.

From the Department of Neurology and Neurosurgery, headed by Dr. Temple Fay, and the Department of Pathology, headed by Dr. Lawrence W. Smith, Temple University School of Medicine and Hospital.

There were marked ataxia and weakness of both upper and lower extremities, and the patient's hands were held like "paddles." Touch, pain and temperature sensation was diminished in the forearms and hands and absent in the lower extremities below the knees. Position sense, vibration sense and graphesthesia were absent in all extremities. Pain sensation was lost below the ninth thoracic and impaired below the fourth thoracic segment. There was a vasomotor level from the fourth to the ninth thoracic segment. There was no pain on pressure over any of the nerve trunks in the arms or legs. The soles of the feet showed slight keratosis.

The patient was obese and dyspneic and showed signs of congestive heart failure. The temperature was from 97 to 98.4 F.; the pulse rate, 60 to 80; the blood pressure, from 110 to 120 systolic and 60 to 70 diastolic.

Laboratory Findings.—On admission repeated blood counts showed that the erythrocytes were at the 5,000,000 level, the hemoglobin content was 13 to 14 Gm., the white cells were between 9,000 and 13,000 and the differential count was normal.

The blood sugar was 87 mg., urea nitrogen 10 mg., serum cholesterol 125 mg. and calcium 10.5 mg. per hundred cubic centimeters. The Wassermann reaction of the blood was negative. The sedimentation rate was 17 mm. per hour.

Urinalysis gave normal results except for a slight trace of albumin.

Gastric Analysis: A fasting specimen showed a total acidity of 75 degrees and no free acid. The first hour specimen showed a total acidity of 75 degrees and 20 degrees of free hydrochloric acid. The patient then vomited the tube, and the procedure could not be repeated.

Spinal Puncture: The initial pressure was 10 mm. of mercury; the Queckenstedt test gave a negative reaction; the protein content was 34 mg. and the chlorides 692 mg. per hundred cubic centimeters; the cell count was 10 (7 lymphocytes and 3 polymorphonuclears) per cubic millimeter; the Wassermann reaction was negative, and the colloidal gold curve was 0111111000.

Consultations.—Cardiac Examination (Dr. J. B. Wolffe): There were arteriosclerotic heart disease, myocardosis and moderate congestive failure (there seemed to be a great deal of induction in the tracings, which may have been due to twitchings of involuntary muscle).

Reaction Degeneration Test (Dr. J. H. Taeffner): There was no change in the muscles of the forearms and hands. The muscles of the legs below the knees responded well to galvanic stimulation, but there was marked quantitative reduction to large faradic currents.

Roentgenographic Examination (Dr. W. C. Hall): Fluoroscopy revealed fixation of the left leaf of the diaphragm.

Teeth: There was an apical abscess of the left upper lateral incisor and the right upper first bicuspid.

Gastrointestinal Series: The findings were normal; the old gastroenterostomy stoma was functioning well.

Diagnosis.—The diagnosis was "polyneuritis," secondary to chronic alcoholism and avitaminosis, probably of the B complex type.

Investigations for Arsenic.—There was no history of exposure to arsenic or heavy metals. The patient had not used any hair tonics. A check of medicaments used revealed no obvious source of arsenic. Nevertheless, a forty-eight hour specimen of urine (1,315 cc.), examined for arsenic by Dr. R. H. Hamilton, of the department of chemistry, contained 0.87 mg. of arsenic trioxide. Examination of the hair and nails also revealed the presence of arsenic.

Three twenty-four hour specimens of urine from ward patients analyzed by Dr. Hamilton showed no arsenic, whereas a specimen of 3 cc. of urine obtained

from a chemist from his department revealed 0.001 mg. of arsenic trioxide, or about 0.43 mg. if calculated for the amount of urine that the patient voided (1,315 cc.).

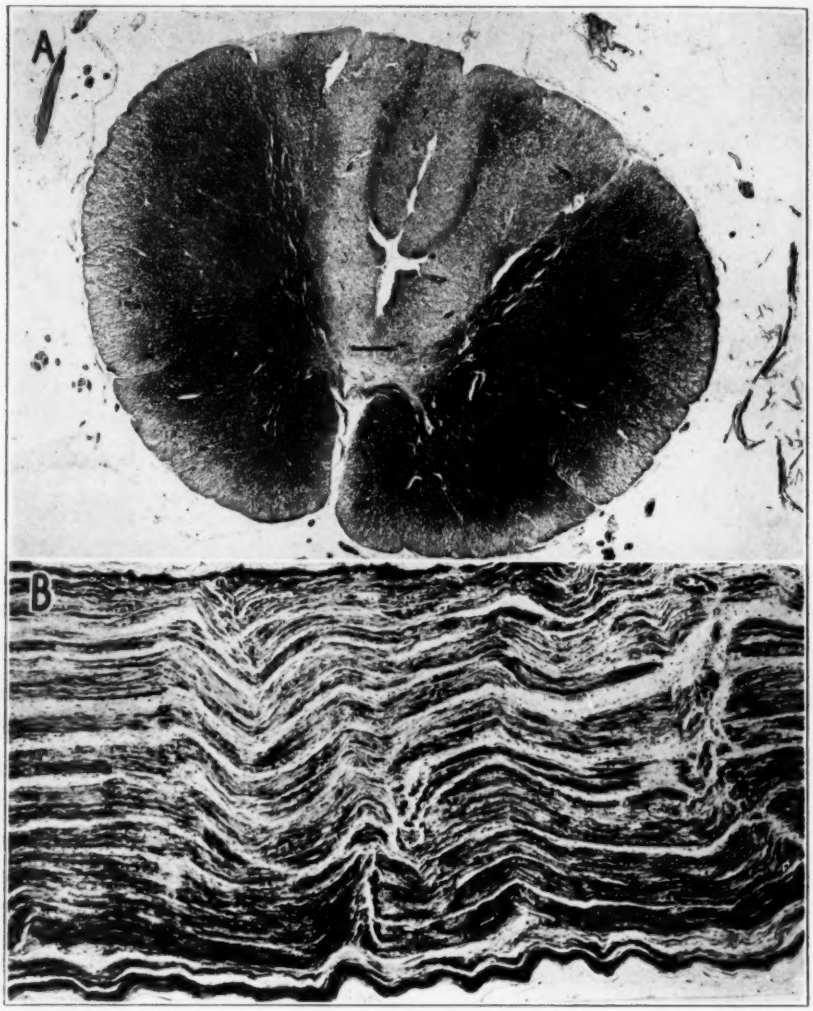

Fig. 1.—*A*, cross section of the thoracic portion of the spinal cord in our case, in which there was an abnormal amount of arsenic in the urine. Note the demyelination of the posterior columns. Compare with figure 2, which shows the lesions in the spinal cord in a case of experimental vitamin B_2 deficiency, and with figure 3, which shows the location of the lesions in the spinal cord in pellagra. Magnification approximately 12. Weil stain.

B, longitudinal section of a peripheral nerve (median) in the same case as that illustrated in *A*. Note the demyelination of the nerve fibrils, and compare with figure 2 *B*. Magnification approximately 50. Weil stain.

Course.—The patient was treated with large doses of brewers' yeast by mouth and liver extract by hypodermic injection. However, he gradually failed; paralysis of the diaphragm developed, and he died on June 10, 1937, seven weeks after admission and approximately nine months after recognizable onset of symptoms.

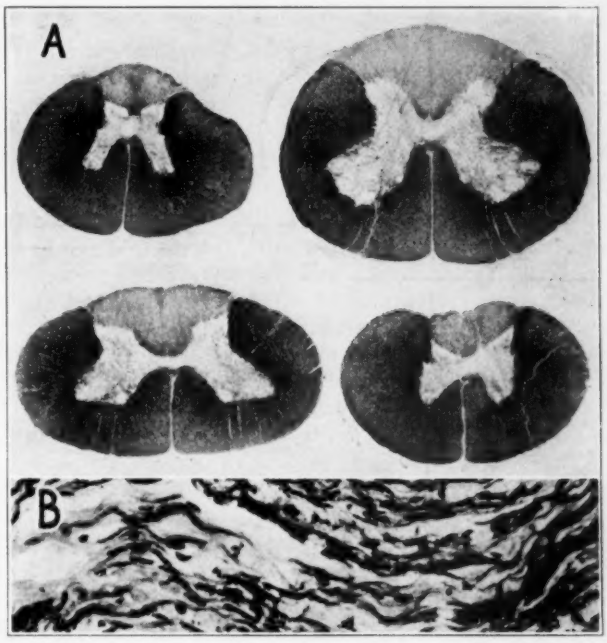

Fig. 2.—Lesions produced in the spinal cord and a peripheral nerve of pigs by diets deficient in vitamin B_2 (from Wintrobe[1b]). *A*, section of the spinal cord, showing pallor of the posterior columns at all levels, indicating loss of myelin. Mahon stain; × 5. *B*, sciatic nerve, showing swelling and fragmentation of axis-cylinders. Compare these experimental observations with those shown in figures 1 and 3.

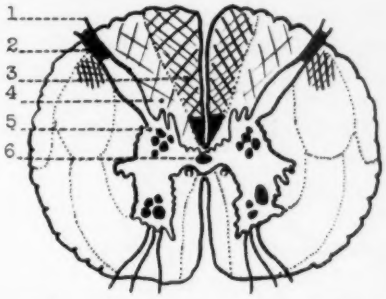

Fig. 3.—Diagrammatic cross section of the spinal cord of a pellagrin. The solid black and cross-hatched parts represent the lesions. *1* indicates the posterior root; *2*, the tract of Lissauer; *3*, Goll's column; *4*, the column of Burdach; *5*, the column of Clarke, and *6*, the central canal (Procupiu, after Babes, in Roberts, S. R.: Pellagra, St. Louis, C. V. Mosby Company, 1912).

Autopsy.—The microscopic changes in the peripheral nerves, spinal cord and brain were identical with those seen and described in cases of pellagra, vitamin B_2 deficiency and chronic arsenical poisoning [1] (figs. 1, 2 and 3).

Microscopic examination of the heart muscle showed advanced myocardosis. The liver was the seat of localized areas of fatty metamorphosis and chronic cholangitis. The pancreas and adrenal glands showed nothing unusual, but were not thoroughly examined. The gastrointestinal tract showed no gross lesions; the old gastroenterostomy stoma appeared normal. Unfortunately, no microscopic studies were made of the gastric or intestinal mucosa. Section of the brain showed moderate injection of the vessels and some dilatation of the fourth ventricle.

COMMENT

There is a great deal of debate as to the "normal" content of arsenic in the urine. Bang (quoted by Barker [2]) found that the arsenic in the urine varies with the foodstuffs and that the excretion may "normally" reach 0.5 mg. daily. Hamilton,[3] however, stated that 0.01 mg. of arsenic trioxide per hundred cubic centimeters of urine is the normal excretion. On the basis of her estimation, our patient should have excreted 0.13 instead of 0.87 mg. Griffon and his associates [4] found in 50 per cent of normal persons examined an excretion of 0.01 to 0.03 mg. of arsenic in twenty-four hours. Even if we use the higher value we find that our patient excreted fifteen times this amount in twenty-four hours. Shelden and Meyers and their co-workers [5] and Carlson expressed the belief that elimination of arsenic in the urine in any amount is of clinical significance, especially if there are symptoms which can be attributed to this element.

CONCLUSION

A case is presented in which the condition could be diagnosed as either pellagra or vitamin B deficiency. An abnormal amount of arsenic was found in the urine. Since chronic inorganic arsenical poisoning produces clinical and microscopic changes similar to those in pellagra

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1. (*a*) Zimmerman, H. M.; Cowgill, G. R., and Fox, J. C., Jr.: Neurologic Manifestations in Vitamin G (B_2) Deficiency: Experimental Study in Dogs, Arch. Neurol. & Psychiat. **27**:286 (Feb.) 1937. (*b*) Wintrobe, M. M.; Mitchell, D. M., and Kolk, L. C.: J. Exper. Med. **68**:207, 1938. (*c*) Dana, C. L.: Brain **9**:456, 1886-1887. (*d*) Henschen and Hildebrand, cited by Bumke, O., and Foerster, O.: Handbuch der Neurologie, Berlin, Julius Springer, 1936, vol. 13, p. 723. (*e*) Chiari, cited by Scott, E., and Reinhart, H. L.: J. Lab. & Clin. Med. **15**:405, 1930.

2. Barker, L. F.: Endocrinology and Metabolism, New York, D. Appleton and Company, 1922, vol. 3, p. 308.

3. Hamilton, A.: Industrial Poisons in the United States, New York, The Macmillan Company, 1925, p. 214.

4. Griffon, H.; Buisson, M., and Bardou, P.: Compt. rend. Soc. de biol. **116**: 478, 1934.

5. Shelden, W. D.; Doyle, J. B., and Osterberg, A. E.: Neuritis from Arsenic and Lead: The Significance of Chemical Studies in Diagnosis, Arch. Neurol. & Psychiat. **27**:332 (Feb.) 1932. Myers, C. N.; Throne, B.; Gustafson, F., and Kingsbury, J.: Indust. & Engin. Chem. **25**:625 (June) 1933.

and vitamin B deficiencies, it is suggested that chronic ingestion of inorganic arsenic may play an etiologic role (primary or secondary) in pellagra and other vitamin deficiencies.

Experiments are now in progress to investigate these factors.

DISCUSSION

DR. F. H. LEWY: I do not understand the conclusion which Dr. Scott draws from his experiments. Does he believe, as I do, that many metallic poisons which produce changes in the nervous system act through interference with elimination?

DR. B. J. ALPERS: Recently I observed a case of arsenical neuritis at the Philadelphia General Hospital. However, I do not understand how one can make a comparison from the similarity between arsenic poisoning and pellagra. One could make the same comparison of diabetes and lead poisoning. Lesions of poliomyelitis and of rabies look alike under the microscope, but they have a totally different mechanism. There is no real evidence, so far as I know, to back the assertion that the heavy metals are concerned with vitamin B metabolism.

DR. MICHAEL SCOTT: There is certainly no proof in this presentation, but what we wished to demonstrate is that there is no question that many symptoms of B avitaminosis can be produced by chronic inorganic arsenic intoxication; before one makes a diagnosis of B avitaminosis or of arsenic poisoning both factors must be considered.

We do not know whether or not the symptoms are due to the possibility that arsenic prevents the absorption of vitamins, but we present this as an interesting suggestion.

SYPHILITIC CEREBRAL HYPERTROPHIC PACHYMENINGITIS

Clinicopathologic Studies in a Case

GEORGE B. HASSIN, M.D.
Professor of Neurology, University of Illinois College of Medicine; Attending Neurologist, Cook County Hospital.
AND
HOWARD ZEITLIN, M.D.
CHICAGO

Hypertrophic pachymeningitis, cerebral or spinal, is a much rarer type of neurosyphilis than the vascular or leptomeningeal forms. In the present case the pathologic process not only involved the larger portion of the cerebral dura and its falx, but extended to the tentorium, pons, medulla and upper portion of the spinal cord. Regardless of such an extensive involvement, the clinical signs and symptoms were meager and, like the histologic changes, were unique.

REPORT OF CASE

History.—A white man aged 44, who always had been in good health, was admitted to the Cook County Hospital on Feb. 26, 1938, because of severe headaches of four months' duration and loss of weight. The headaches were frontal, occasionally occipital, and were especially severe in the evening, when they would become "sharp" and increase on coughing. About three and one-half months after the onset of the headaches, the patient commenced to experience difficulties in swallowing, which necessitated nasal feeding.

The patient denied having smoked or used alcohol immoderately or having had acute or chronic infectious diseases, such as syphilis or tuberculosis. He had been married eighteen years; his wife had had three miscarriages.

Examination.—The patient was emaciated and exhibited a profuse discharge from the right nostril, from which a catheter protruded. There were no anomalies of speech or signs of paralysis or paresis of the extremities. There was slight tenderness over the skull below the occiput and over the frontal region. The neck was somewhat rigid, and a slight Kernig sign could be elicited on the left. The pupils were small (about 2 mm.); the left pupil was somewhat irregular; both reacted to light and in accommodation. There was bilateral papilledema (1 D. in the right and 1.5 D. in the left eye). There were weakness of the lower branch of the left facial nerve and deviation of the tongue to the left, without atrophy or tremor, and occasional deviation of the uvula to the left (to the right, according to one note). The hearing, ocular movements, coordination, reflexes, sensibility and genitourinary

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Read at the Annual Meeting of the American Association of Neuropathologists, Atlantic City, N. J., June 5, 1939.

From the Department of Neurology and Neurological Surgery, University of Illinois College of Medicine, and the Neurologic Service of the Cook County Hospital.

organs exhibited no abnormalities. Nothing pathologic was elicited in the heart, lungs or bones, and the mental condition of the patient was normal.

Laboratory Data.—The spinal fluid was clear and colorless. The pressure was 28 mm. of water, which was not elevated by pressure on the left jugular vein but was increased by pressure on the right. Bilateral pressure caused a rise of 3 cm. The Pandy reaction was 3 plus, and there were 89 lymphocytes per cubic millimeter; the Wassermann reaction, of both the blood and the spinal fluid was negative. The Lange curve, determined in another hospital, according to information given by Dr. J. A. Luhan, was 5543211000 in one instance and 4555543210 in another.

Examination of the blood showed 3,800,000 red cells and 7,500 white cells per cubic millimeter, and the hemoglobin concentration was 90 per cent.

Roentgen examination disclosed "very coarse and mottled architecture of the calvarium"

Examination three days after admission revealed a Horner syndrome on the left, distinctly nasal speech, engorged veins in the fundi and linear hemorrhages beside the disks.

Diagnosis.—On the basis of the findings outlined, a diagnosis was made of unilateral lesion of the ninth, tenth and twelfth nerves, caused probably by tumor or adhesive arachnoiditis, with resulting involvement of the basal cisterns and papilledema.

Course.—From March 8 to 19 the patient was given antisyphilitic treatment (mercury by inunction and potassium iodide). There was improvement in the general health and headaches, and the patient voluntarily left the hospital on March 20.

Improvement lasted only one week. As the headaches grew worse again, the patient willingly submitted to suboccipital decompression, which was performed two weeks later in another hospital. He returned to the Cook County Hospital on May 2, with the old complaints. Examination revealed a pulsating mass in the occipital region, the "size of a ball"; bilateral papilledema (1 and 1.5 D.); normal visual fields; a somewhat rigid neck; a "chain of glands" on both sides of the neck, extending posteriorly to the sternocleidomastoid muscles; scaphoid abdomen, and slight dulness in the apex of the left lung. A roentgen examination of the left jugular foramen and of the skull disclosed signs of a previous operation over the occiput, but nothing suggestive of a tumor that might have pressed on the nerves passing through the jugular foramen, or of increased intracranial pressure.

For the next six months the condition remained almost stationary—only the headaches grew worse, especially in the evening, when they were severe enough to make the patient groan. For the most part he lay quiet and showed no interest in the surroundings; he took nourishment, and occasionally was irritable when he was disturbed. The temperature and pulse and respiration rates were always within normal limits.

Treatment was symptomatic, sometimes in the form of intravenous injections of hypertonic solutions of dextrose.

He died in November 1938 of bronchopneumonia, almost a year after the onset of the illness.

Gross Necropsy Observations.—There were: lobar pneumonia of the right upper and lower pulmonary lobes; confluent bronchopneumonia of the left lower pulmonary lobe; brown atrophy of the liver and myocardium; fatty degeneration

of the intima of the aorta and hyaline fatty plaques, and moderate sclerosis of the coronary arteries, their lumens being somewhat narrowed and their thinned walls containing calcified plaques.

The brain weighed 1,500 Gm.; its convolutions were flattened, and the sulci were shallow. The dura was thickened over the cerebellum and the occipital lobe (fig. 1 *B*); it was easily detachable from the underlying arachnoid, but was adherent to the base of the cranium. The tentorium was 8 mm. thick; over the lateral lobes of the cerebellum the dura was from 2 to 4 mm. thick. The thickened dura extended from the occipital to the parietal lobe (fig. 1 *C*), the thickness gradually receding cephalad, but was normal over the frontal area (fig. 1 *D*). The outer surface of the dura was smooth and glistening; the inner layer was rough and uneven. Over the left parietal lobe, 1.5 cm. lateral to the longitudinal sinus and behind the posterior central convolution, the dura contained a thin, almost transparent, parchment-like patch, its size being 2.5 by 4 cm. It is shown in a transverse section in figure 1 *E*.

The walls of the longitudinal sinus were from 4 to 6 mm. thick, but only in the portion extending as far as the posterior central convolution; the lumen was

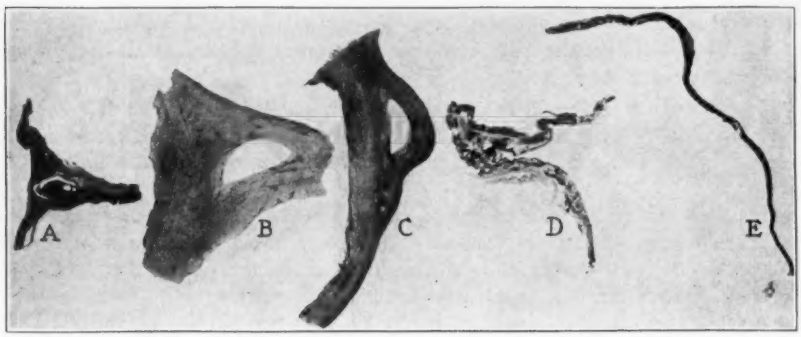

Fig. 1.—Transverse sections of the dura and the enclosed longitudinal sinus at various levels, all taken under the same magnification (× about 2). *A* shows a normal dura and sinus. A thickened dura from the occipital region in the present case is shown at *B*, from the parietal area at *C*, from the normal frontal area, at *D*, and from the thinned, parchment-like patch, at *E*. The contrast between *B* (reproduced under higher magnification in figure 2) and *E* (reproduced under higher magnification in figure 4 *B*) is evident.

narrowed, but the lumens of the straight and lateral sinuses were practically obliterated. The optic chiasm and the adjacent area, including the cerebral peduncles, adjacent third nerve and blood vessels, were normal. The pons was reduced to about one-half its size; its left margin was depressed and was represented by a niche. A similar depression was present over the left margin of the medulla. The condition of the nerves of the medulla could not be ascertained, as they had evidently been torn away in the process of removal of the brain. The cerebellum appeared collapsed, as though it was compressed by the thickened dural membrane, and the right cerebellar lobe was almost one-half the size of the left.

Coronal sections of the brain disclosed no changes except dilatation of the left lateral ventricle.

Microscopic Observations.—The dura, under a magnifying lens, exhibited stripes, as if it was made up of several pseudomembranes (fig. 2). The youngest pseudomembrane bordered the lumen of the sinus (at *A*), which it encircled in the form of a pale ring. The other pseudomembranes consisted of bands of collagenous fibrous tissue, the spaces of which were infiltrated chiefly with plasma cells, mixed with lymphocytes, mast cells and fibroblasts. Some interstitial spaces were minute and harbored only a single row of plasma cells. Other spaces were wider and contained several rows of cells, with occasional dense conglomerations of lymphocytes and

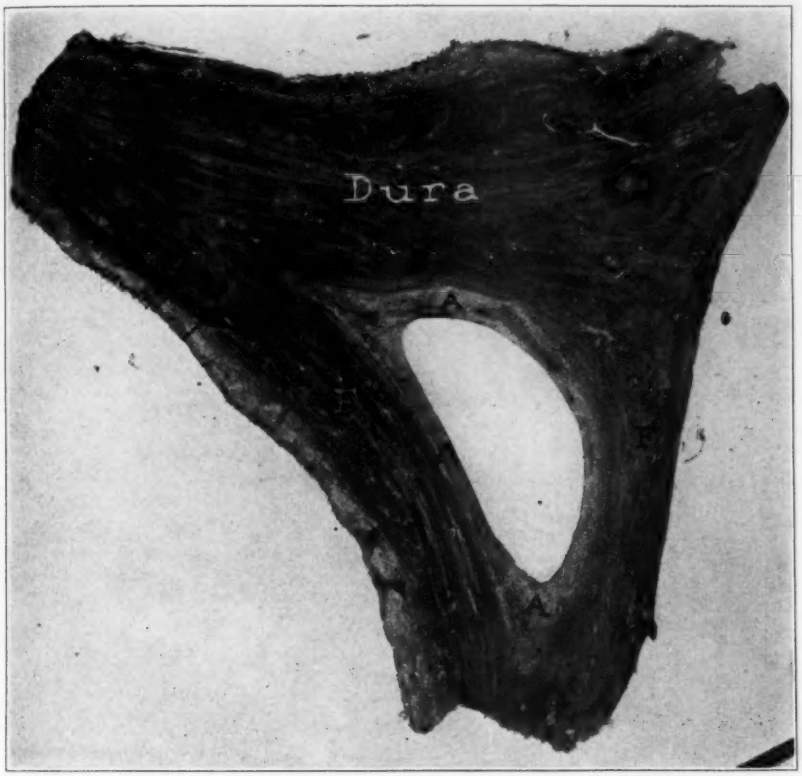

Fig. 2.—The thickened dura shown in figure 1 *B*. At *A* is a pseudomembrane which has not developed into the solid pseudomembranes divided by stripes seen above and lateral to the lumen of the sinus. *FF*, the falx, contains the sinus (empty). Van Gieson stain; × about 7.4.

plasma cells. These were usually adjacent to or closely connected with a blood vessel. In figure 3 *A*, for instance, two such infiltrated bands are seen continuous with the hyperplastic tunics of a blood vessel. The infiltrations are still better exhibited in figure 3 *B*, which represents a surface (longitudinal) section of a dural pseudomembrane. Such infiltrations sometimes formed dense nodules (fig. 4 *A*), which seemed to constitute an integral part of the adjacent blood vessel, as if fused with its infiltrated walls. The infiltrations were present throughout the dura, even in its thinnest filiform portion (fig. 4 *B*). The infiltrating cells of the blood vessels

were of the same type as those of the adventitial spaces (mainly lymphocytes and plasma cells). The infiltrations were diffuse; that is to say, they formed no nodules but extended over all the tunics, giving a picture of panarteritis or gummatous periarteritis. The familiar infiltrations of the Virchow-Robin spaces were not in

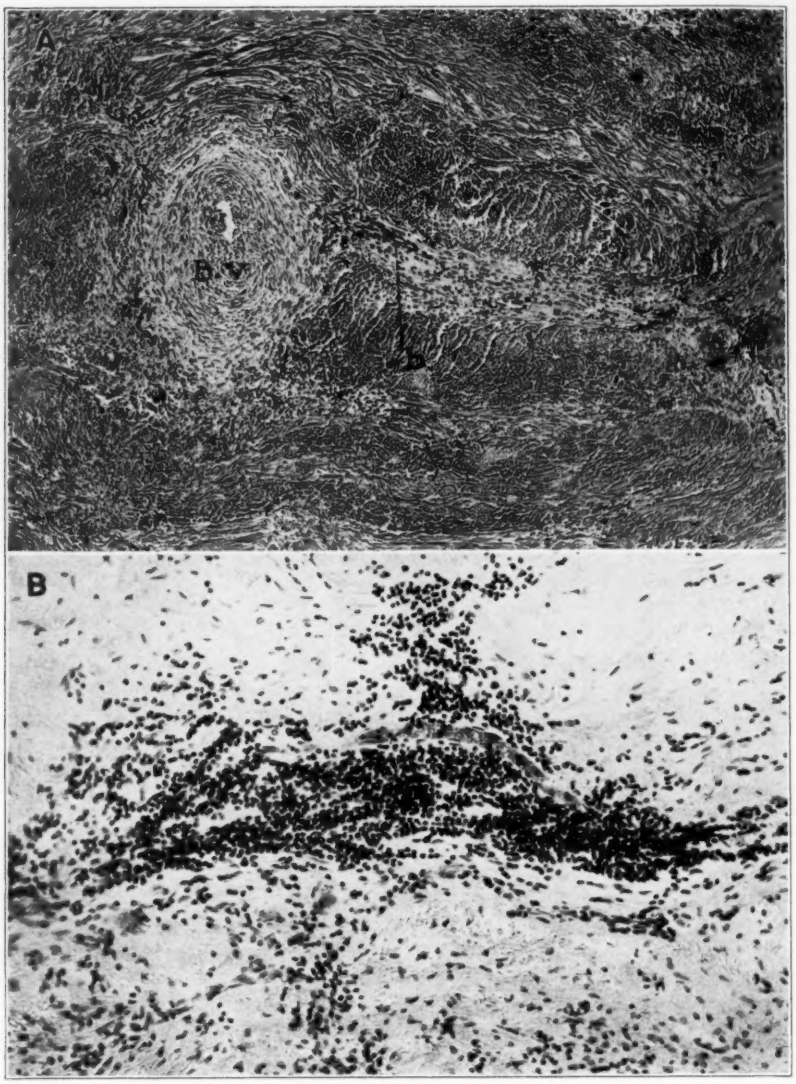

Fig. 3,—*A*, in the center (*BV*) is a blood vessel, the lumen of which is narrowed and the walls hyperplastic and thickened. At *b* infiltrated bands can be seen extending from the blood vessel for a great distance. × 75.5. *B*, surface section showing gummatous infiltration of a dural pseudomembrane described in the text; × 136. Van Gieson stain.

evidence, as such formations in the dural blood vessels evidently do not exist. The vascular walls were not only infiltrated but also often hyperplastic (fig. 3 *A*), their lumens narrowed but not occluded. The elastic membrane was definitely split, and its broken up fibrils were scattered throughout the layers of the vessel wall. In

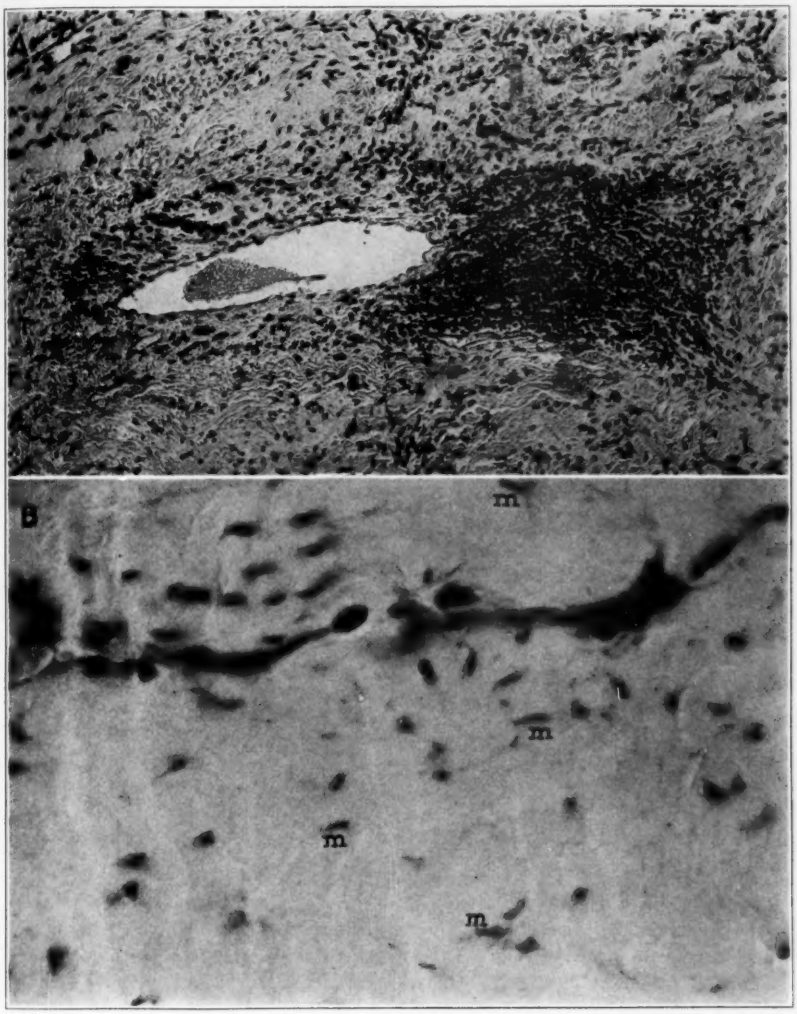

Fig. 4.—*A*, miliary gumma, a dense focus to the right of the wall of the blood vessel, with which it is fused and the left half of which is infiltrated. *B*, the filiform portion of the dura (*E* of figure 1). The capillary is infiltrated with lymphocytes and plasma cells; the rest of the visual field is covered with fibroblasts and microgliocytes (*m*). A magnifying hand lens should be used. × 688. Van Gieson stain.

general, blood vessels were scarce in the pseudomembranes, but were numerous around the lumen of the sinus in the young pseudomembrane. Here, fully developed connective tissue was less in evidence than in the older pseudomembranes. The connective tissue here consisted of meshes of slender fibers and immense masses of blood vessels which were distended with blood, while the meshes contained enormous infiltrations of plasma cells chiefly, among which was an occasional giant cell (fig. 5). This pale, colorless pseudomembrane seems to represent a younger stage of a dural pseudomembrane, which evidently was being formed continually and probably would have ultimately resulted in complete occlusion of the sinus. On the other hand, the parchment-like filiform portion of the dura (figs. 1 *E* and 4 *B*) consisted

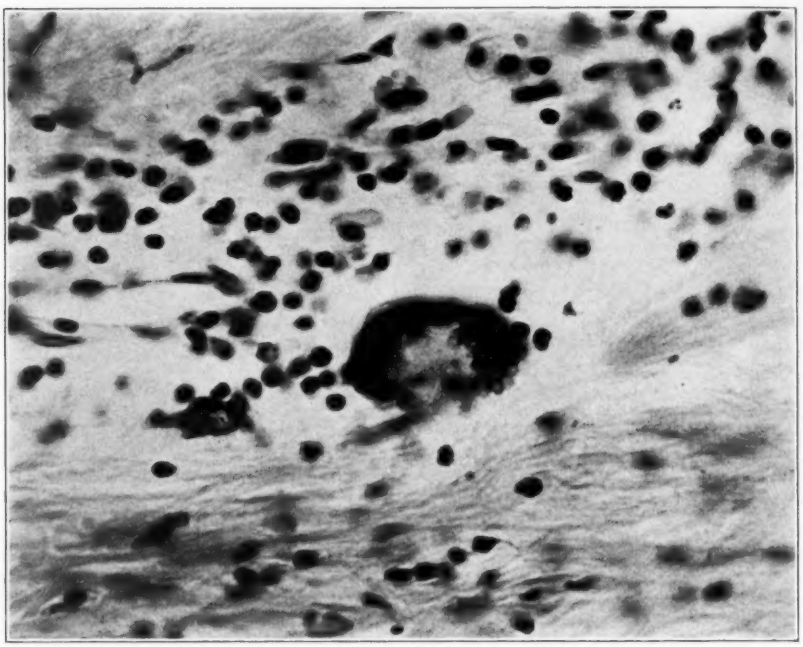

Fig. 5.—The infiltrating cells of a pseudomembrane—mostly plasma cells, among which a giant cell is in evidence. × 590.

for the most part of collagen fibers, the most superficial of which appeared as homogeneous strands. As figure 4 *B* shows, there were hardly any infiltrations. The few cells seen there, mainly in the vicinity of the long capillary, were lymphocytes and plasma cells, but the majority of the cell elements covering the visual field were fibroblasts and microgliocytes. Some of the latter are faintly reproduced in figure 4 *B*, *m*. Lacunas were absent; elastica fibers were scarce, and blood vessels were practically absent. The histologic picture was that of a scar formation and differed entirely from that presented by the innermost pseudomembrane of the dura.

The portions of the dura which normally contain lacunas were deprived of them. They evidently were obliterated by the hyperplastic growth of the dura. They were present, however, in the parts of the dura that were only slightly involved, but were devoid of contents and infiltrated masses. The arachnoid membrane was well

preserved. The villi were well developed, but they did not invade the dura or sinuses and were covered by thick layers of mesothelial cells, which separated the villi from the lumen of the sinus.

The pia was densely infiltrated throughout with lymphocytes and plasma cells, which in some areas, especially over the cerebellum and the occipital area, formed a conglomeration which resembled so-called miliary gummas.

The spinal dura exhibited changes similar to those described: thickening; infiltration of the interstitial dura spaces with plasma cells, mast cells and lymphocytes; extension of the infiltrations to the vessel walls, septums and spinal roots, and numerous microglia cells in areas devoid of hematogenous infiltrations. In short, the histopathologic features here were analogous to those seen in cervical hypertrophic pachymeningitis.

Changes in the Parenchyma.—As has been stated, the medulla and pons exhibited excavations or niches on their left lateral surface. These areas were, on microscopic examination, sparsely covered with fat granule bodies, which were mixed with microgliocytes and swollen oligodendrogliocytes, the nuclei of which were in many instances disrupted (karyorrhexis). In general, the ganglion cells were normal; only a few exhibited changes of so-called acute cell disease, or liquefaction, satellitosis or neuronophagia. The blood vessels in the pons and medulla were normal; there were newly formed capillaries with hypertrophied endothelium. Analogous changes were present in the brain substance, where, however, no fat granule bodies were observed. Occasional infiltrations of the blood vessels with lymphocytes and plasma cells were present only in the basal ganglia, and in the occipitoparietal portion of the brain miliary gummas were in evidence.

The gray substance of the spinal cord was unchanged. It contained numerous microgliocytes, especially in the posterior horns, while the white substance of the uppermost portion of the spinal cord exhibited reactive glial and neuroglial phenomena, with slight lymphocytic infiltrations of the spinal roots.

Nothing pathologic was seen in the middle and lower portions of the spinal cord, nor were spirochetes demonstrated in the brain substance or meninges.

Summary of Histopathologic Observations.—There were vast hematogenous infiltrations of the dura and pia with formation of miliary gummas; hematogenous infiltrations of the walls of the blood vessels in the form of panarteritis; enormous hyperplasia of the caudal part of the cerebral dura, including the cerebellar portion and the tentorium, and thinning of a small segment of its rostral portion; unilateral scattered degenerated areas of the pons and medulla, and relatively mild and limited involvement of the brain substance. The changes outlined, some of which were definitely syphilitic, may explain the unilateral bulbar phenomena, the condition of the fundi and the unsatisfactory response to the treatment.

COMMENT

The immense infiltrations, especially of the dural interstitial spaces, with plasma cells; the panarteritis with the general hyperplasia of the vessel walls; the breaking up of the elastica membrane; the association of the diffuse meningeal infiltrations with hypertrophy of the walls of the blood vessels; the miliary gummas and giant cells, all denote a chronic inflammatory syphilitic process. Some of the changes outlined occur also

in tuberculous lesions of the brain, but miliary gummas and the vascular changes of the type here described speak against tuberculosis. In tuberculous pachymeningitis the destructive phenomena are much more extensive, for the tubercles, small as they are, generally undergo rapid and more extensive destruction in the form of cheesy degeneration. We have not observed cheesy degeneration of a miliary gumma.

A thickened, hypertrophied dura is usually blended with the underlying membranes—obliterating the subdural and subarachnoid spaces—and through them with the cerebral parenchyma, which is transformed into a mass of gummas, blood vessels and mesodermal tissue. One has the impression that the syphilitic process travels from the dura to the subjacent structures, as if the meningeal tissues become affected successively and ultimately result in the destruction of the cerebral parenchyma. In the present case, blending of the meninges with each other and with the brain was not present; the process was localized and was especially manifest in the dura, while the pia-arachnoid evidently became involved independently. The changes in the pons and medulla, however, were due to pressure by the enormously thickened dura. That gradual pressure of long standing may cause degeneration and atrophy of brain tissue has been demonstrated elsewhere.[1]

A striking phenomenon was the localization of the pachymeningitis. There exists no record in the literature of such an extensive dural thickening, which included the tentorium. In the case of Homén [2] the gummatous pachymeningitis covered the major part of the right parietal lobe, the central convolutions, the upper portion of the right temporal lobe, the anterior part of the occipital lobe and the corresponding basilar portions of the brain. In addition, there were tumor masses underneath the dura which contributed to the thickening of the dura.

While in our case the longitudinal sinus was patent, the straight and lateral sinuses were, as has been noted, almost obliterated, and nowhere did the arachnoid villi pierce the dura. The hypertrophied dura prevented their invasion of the sinuses and the supposed discharge of their contents, the cerebrospinal fluid. The villi, however, showed no evidence of distention or retention of the cerebrospinal fluid, which would have been the case if the dominant teaching that it is absorbed by the villi were correct.

While the academic value of study of cases of syphilitic pachymeningitis is great, the practical value is not, except possibly with respect to the role basilar pachymeningitis may play in causing bulbar paralysis. The formidable scar into which the dura had been transformed rendered the prognosis hopeless even if the condition had been recognized and vigorously treated. Fortunately, cases of cerebral hypertrophic pachymeningitis are rare, only 2 other instances of this morbid condition having

1. Hassin, G. B.: Changes in the Brain in Increased Intracranial Pressure, Arch. Neurol. & Psychiat. **20**:1172 (Dec.) 1928.

2. Homén, E. A.: Zur Kenntnis der grossen meningealen und Gehirngummata, sowie der Rückenmarksyphilis, Arch. f. Dermat. u. Syph. **46**:55, 1898.

been observed by one of us (G. B. H.) [3] among 1,700 brains studied. Only 5 contributions [4] dealing with this type of syphilis could be found. Oppenheim [5] did not even mention this type of syphilis in his large monograph, and Nonne [4a] discussed it under the heading of fibroplastic meningitis.

As to the genesis of the pseudomembranes, one must assume that when an infection invades so powerful a membrane as the dura, an intense reaction on the part of the mesodermal elements (blood vessels and connective tissue) must result. Hemorrhages undoubtedly play a role, as had been emphasized elsewhere.[4d]

CONCLUSIONS

Cerebral hypertrophic pachymeningitis may cause multiple involvement of the cranial nerves and give a picture of bulbar paralysis.

The disease is a malignant form of neurosyphilis which is usually not recognized clinically and, if suspected, does not yield to treatment.

It is in all probability a specific form of neurosyphilis, differing from the meningeal or vascular type.

DISCUSSION

DR. LEO ALEXANDER, Boston: A similar case was observed recently by Dr. Jerry Price, at the Boston City Hospital. The distribution of the thickening, involving particularly the tentorium and dura of the posterior fossa, was strikingly analogous to that which Dr. Hassin described so impressively. Clinically, in this case endocrine disturbances at one time suggested the clinical diagnosis of hypophysial neoplasm. Study of the hypophysis and surrounding dura has not yet been completed. I wish to ask Dr. Hassin whether any endocrine abnormalities have been present in his cases.

DR. GEORGE B. HASSIN, Chicago: The case of Dr. Alexander should be of great interest, as this type of syphilitic meningitis is rare. Endocrine abnormalities were not present in my case. In the cases which I described [3] the dura, pia-arachnoid and brain tissues, as a whole, were fused together; I wonder whether this fusion occurred also in the case mentioned by Alexander, for it is not mentioned in the literature.

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3. Hassin, G. B.: Histogenesis of Cerebral Hypertrophic Pachymeningitis, Am. J. Syph. **2**:715, 1918.

4. (*a*) Nonne, M.: Syphilis und Nervensystem, ed. 4, Berlin, S. Karger, 1921. (*b*) Foerster, E.: Die Syphilis des Zentralnervensystems, in Lewandowsky, M. H.: Handbuch der Neurologie, Berlin, Julius Springer, 1912, vol. 3, p. 365. (*c*) Sézary, A.: Classification des méningites syphilitiques, J. méd. franç. **7**:201, 1913. (*d*) Hassin, G. B.: Histogenesis of Cerebral Hypertrophic Pachymeningitis, Am. J. Syph. **2**:715, 1918. (*e*) Homén.[2]

5. Oppenheim, H.: Die syphilitischen Erkrankungen des Gehirns, in Nothnagel, H.: Specielle Pathologie und Therapie, Vienna, Wilhelm Braumüller, 1902, vol. 9.

FOLIE À DEUX

Report of a Case of Remission from a Psychosis of More Than Twenty-Five Years' Duration

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A considerable number of cases of folie à deux have been reported since Lasègue and Falret first described this condition in 1877.

This case is considered to be worth reporting and of special interest since, after an illness of more than twenty-five years, remission occurred in the psychosis of the submissive one of the pair after the death of the one who had been the dominant personality. Remission from a psychosis of more than twenty-five years' standing is rather spectacular!

REPORT OF CASE

History.—M. O., the mother, active factor, and L. O., the daughter, the passive factor, were admitted together to the Columbus State Hospital on Sept. 11, 1911. Little is known of their early history. The mother was 56 at the time of admission, and the daughter, 23. They were sent to the hospital on the complaint of practically all their neighbors. A sister of the mother was said to have been psychotic, and another sister, a college graduate, was eccentric and had an imbecile child.

M. O., had been married and divorced. There were two or three other children, sons, but little information could be obtained about them. Both patients were reticent and evasive. M. O., with her daughter, had resided in the suburbs of a small town, in a cottage owned by her. In addition to this property, she apparently had enough money to live on. They kept to themselves and did not associate with neighbors, and the mother would not allow the daughter to associate with other children. They kept their house closed, with the shutters also closed. They always went out together, walking about the streets of the town, making their small purchases together and returning home. They would go to the railroad station and other out-of-the-way places and sit for hours on a bench together, talking in whispers. Their eccentric behavior aroused the suspicion of neighbors, and anything they did or said may have been exaggerated. There is no doubt, however, that they gave the neighborhood plenty to talk about because of their peculiar actions. The neighbors had said that the two sang for hours to one of the neighbor's pigs. Questioned about this, the mother said: "Those pigs were in a sty just across from our back fence. If my daughter and I wished to go down and look at them, it was nobody's business, as we were harming no one. If while looking at them we sang for our own pleasure, no one was hurt." Other accusations were made against them which they explained in circumstantial and unreasonable ways. The neighbors charged that the two disturbed them by hammering on their porches, by annoying passers-by and by accusing them of stealing. The mother also accused various ones of making improper advances to the daughter.

Course.—During their residence in the hospital the two made a fairly good adjustment, although they occasionally came into conflict with other patients

because of their paranoid tendencies. They were always together. Neither would even go down the hall to the toilet alone. One would not take a laxative unless the other did. When not employed, they sat together in their room whispering for hours at a time, even to the early hours of morning. One wondered what they found to whisper about, year in, year out. They did good work in the laundry and in the sewing department. They were permitted to attend a nearby church where they were considered eccentric but not intolerable. Systematized delusions were never brought out, but definite paranoid tendencies were evidenced in both. For example, they would complain at times that other patients made faces at them, that they were discriminated against by attendants, and they otherwise revealed persecutory trends. The mother always appeared to be the spokesman and the dominant personality.

On Feb. 17, 1936, after a few days' illness, the mother died. The daughter reacted in a normal way to the death. In a short time, however, there was a change in her attitude and manner. She became friendly and began to talk about wanting to leave the hospital. Some people in the church which she attended became interested in her and requested her release. This was granted on May 4, 1937. Shortly after leaving the hospital she secured employment doing housework for a private family. This family has been pleased with her services and has reported that it has observed nothing abnormal about her. She has been away from the hospital for over two years and has adjusted herself normally. She can at least be considered a social recovery.

COMMENT

Both these patients would doubtless have been considered schizophrenic by most psychiatrists. Their paranoid tendencies, egocentricity, limited contact with their environment, asocial traits and peculiar behavior point to this diagnosis.

Today there is much discussion about, and a leaning toward, the view that schizophrenia is essentially an "organic psychosis." A case such as this does not disprove the thesis, but it emphasizes the importance of psychologic and environmental factors. Schizophrenia may be "organic" in the sense that a certain type of physical organization or constitution, or a type of physiologic dysfunction, may be prerequisite to the development of the disease. Cases such as that reported here, however, indicate that diathesis, lesions or disturbed physiologic functioning cannot be the sole cause in all cases which one now considers as belonging to the schizophrenic syndrome.

In giving a prognosis in a case of mental disease, psychiatrists are often influenced, probably correctly, by consideration of hereditary factors. The recovered member of this pair suffering from folie à deux would certainly have been considered to have bad heredity. Her recovery after the removal of the motivating factor in her psychosis suggests that in some cases environmental influences and early conditioning may be decisive in the development of a mental disorder, even in the presence of strong hereditary factors.

Abstracts from Current Literature

Anatomy and Embryology

THE CENTRAL CONNECTIONS OF THE VESTIBULAR PATHWAYS. WALTER E. DANDY and PAUL A. KUNKEL, Am. J. M. Sc. **198**:149 (Aug.) 1939.

Dandy and Kunkel in 10 experiments on 9 adult cats and 1 adult dog, demonstrated the following: (1) Section of either auditory nerve resulted in frequent spells of violent whirling with rolling to the side of the lesion; (2) section of both auditory nerves resulted in violent whirling with turning to either side; (3) removal of one-half the cerebellum did not produce rotary movements; (4) removal of the entire cerebellum did not cause whirling; (5) section of one auditory nerve and removal of the cerebellar lobe on the same side caused violent rotation and whirling to the same side; (6) section of one auditory nerve and removal of the opposite cerebellar hemisphere did not produce whirling. The difference between section of either or both auditory nerves and removal of half or all of the cerebellum was that in the former procedure terrific whirling of the body resulted and continued until death occurred from exhaustion, while in the latter the animal lay quietly. In man the aberrations of vestibular function are transferred to, and translated by, the visual tracts, so that the effect produced is subjective and visual; in animals the untoward effect is somatic and objective. A surprising feature of the experiments was that bodily rotation after section of one auditory nerve was not affected by removal of the ipsilateral half of the cerebellum, but was abolished by removal of the contralateral cerebellar hemisphere. This means that the vestibular pathways decussate like the pyramidal tracts.

MICHAELS, Boston.

THE RESPONSES TO LIGHT IN THE EARTHWORM, PHERETIMA AGRESTIS GOTO AND HATAI, WITH SPECIAL REFERENCE TO THE FUNCTION OF THE NERVOUS SYSTEM. CHARLES D. HOWELL, J. Exper. Zoöl. **81**:231 (July) 1939.

The earthworm Pheretima agrestis reacts negatively to all intensities of light to which it responds. Excessive mechanical stimulation and high temperature decrease the negativity, probably by producing reactions which inhibit the response to light. Sensitivity of the body to light decreases posteriorly. All operations on the anterior part of the nervous system decrease the degree of negativity to lateral illumination. Removal of the brain, or cutting both circumpharyngeal connectives or the transverse commissure of the brain, causes the worm to respond positively in weak light, although it still responds negatively in strong light. Cutting one circumpharyngeal connective increases the percentage of negative responses to illumination on the side of operation. Photoreceptor cells are present in the epidermis. Nerve impulses aroused by photic stimulation of these cells probably cross in the transverse commissure of the brain or in the commissures of the ventral nerve cord and go to the muscles of the side opposite that which was illuminated. Contraction of these muscles thus produces a negative response.

WYMAN, Boston.

FURTHER OBSERVATIONS ON THE ORIGIN OF THE SHEATH CELLS OF SCHWANN. S. R. DETWILER and KATHRYN KEHOE, J. Exper. Zoöl. **81**:415 (Aug.) 1939.

To determine whether the sheath cells of Schwann in urodeles arise entirely from the cord (Raven) or from the neural crest (Harrison), experiments were performed on early neurulas of Amblystoma (Harrison's stages 14 and 15).

Vital dyes (nile blue sulfate and neutral red) were applied to the neural crest and medullary plate, and the distribution of these dyes was studied later in embryos which survived. Positive evidence was obtained favoring origin of the sheath cells from the neural crest. The conditions also pointed to migration of crest cells across the midline. There was no evidence that the early formed sheath cells wander out from the cord along either the dorsal or the ventral nerve roots. The results did not exclude the possibility of an origin of sheath cells from the cord and their migration along nerve roots in later stages of development. The view that crest cells contribute to the formation of dermal elements of the skin was supported.

WYMAN, Boston.

ANATOMICOEXPERIMENTAL CONTRIBUTION TO STUDY OF THE SUPRAOPTIC COMMISSURES. M. A. GEREBTZOFF, J. belge de neurol. et de psychiat. **39**:320 (May) 1939.

Gerebtzoff studied the supraoptic commissural system in the rabbit by the Marchi method, and as a result of his observations made the following classification: (1) the dorsal supraoptic commissure, or commissure of Ganser, consisting of a dorsal or hypothalamic part and a ventral portion which connects the subthalamic nuclei; (2) the ventral supraoptic, or tectometathalamic, commissure, consisting of a dorsal acoustico-optic portion, or commissure of Meynert, which has its origin in the posterior corpora quadrigemina and the nucleus of the lateral lemniscus and its termination in the dorsal nucleus of the corpus geniculatum laterale, and a ventral optico-acoustic portion, or commissure of Gudden, which has its origin in the anterior corpora quadrigemina and its termination in the dorsal nucleus of the corpus geniculatum mediale.

DE JONG, Ann Arbor, Mich.

NORMAL AND ABNORMAL DEVELOPMENT OF THE CENTRAL NERVOUS SYSTEM IN LIGHT OF RECENT EXPERIMENTS ON AMPHIBIANS. GIAN TÖNDURY, Schweiz. Arch. f. Neurol. u. Psychiat. **43**:360, 1939.

The law of specificity of germ plasm does not apply in the early period of gastrulation, at least not for the ectoderm. The presumptive anlage for the medullary plate when transplanted at this stage to other parts of the embryo may enter into the formation of epidermis or derivatives of other germ layers. The transplanted dorsal lip of the stomodeum, on the other hand, is capable of inducing at its new site formation of a secondary stomodeum and a secondary neural tube. The author has found that when the dorsal lip of the stomodeum is removed by microsurgical methods from a Triton embryo in the early stages of gastrulation, malformations of the head result in 80 per cent of the experiments. In 26 per cent of the cases in which there were developmental anomalies the telencephalon and diencephalon, including the eyes and olfactory bulbs, failed to develop and the hindbrain remained in a more or less rudimentary state. In 39 per cent of cases the various parts of the brain and the sense organs were differentiated but smaller than normal, while in 35 per cent malformations were relatively slight and were limited to the forebrain. Microscopic sections of embryos with marked arrest of cephalic development showed complete absence of the foregut and of material normally making up its roof, the endoderm being represented by a collection of yolk-containing cells. Study of embryos with less marked defects revealed a close correlation between malformations of the brain and faulty development of the foregut and its roof. These experiments indicated that the brain and sense organs were dependent for their normal development on the proper differentiation of endomesodermal elements.

Immersion of an Axolotl embryo in Ringer's solutions of high osmotic value during the first stage of gastrulation has been shown to inhibit the process of invagination. When complete "exogastrulation" results, a neural tube fails to develop. On the other hand, the more completely material of the marginal zone

invaginates, the greater is the degree of ectodermal differentiation. Not only a spinal cord but even a head and eyes, which are somewhat smaller than normal, may develop. A medullary plate removed in the early stages of gastrulation and cultured in Ringer's solution develops into a mass of indifferent cells, whereas material from the dorsal lip of the stomodeum is capable under similar conditions of forming a notochord and primitive mesodermal segments. When embryos in the early stages of gastrulation are treated with solutions of lithium chloride, the prechordal plate does not develop normally, and the roof of the foregut fails to differentiate into a notochord and primitive segments. Associated with these anomalies are closely corresponding defects in the overlying neural tube, amounting at times to complete anencephaly. The olfactory bulbs may be undivided or be lacking entirely, while the optic vesicles may be approximated to varying degrees and may even be fused (synophthalmos). With defective development of the rhombencephalon the auditory vesicles may be abnormally small and lie close together in a ventral position, as in otocephalic monsters.

When an ovum from Triton palmatus or taeniatus is deprived of its nucleus and is fertilized with the sperm of Triton cristatus, gastrulation will proceed, but formation of the neural tube is delayed and normal cephalic development is disturbed. Regressive changes occur in the mesoderm, and by the time the neural tube has closed prechordal material may have entirely disappeared.

Malformations of the brain and sense organs encountered in man and other mammals are known to be associated with defects in derivatives of the prechordal plate and the foregut. In addition to defective development of anterior portions of the brain, cranial anomalies, consisting principally in absence of the ethmoid bone and malformation of the sphenoid bone, are characteristic of cyclops and arhinencephaly. Malformations of the mouth, including complete absence of the lower jaw, on the other hand, are seen in cases of otocephaly. Save for a highly defective occipital bone, the skull is entirely lacking in anencephalic guinea pigs. In conclusion, the view is expressed that malformations of the brain produced experimentally in amphibians are analogous to similar malformations seen in higher forms; that in both instances the malformations are due primarily to defective development of underlying tissues making up what the author terms the "head organizer." The spontaneously occurring monstrosities are attributed to various noxae which act primarily on the "head organizer."

DANIELS, Denver.

Physiology and Biochemistry

FUSIONAL MOVEMENTS. HERMANN M. BURIAN, Arch. Ophth. **21**:487 (March) 1939.

Burian states that all investigations concerning the fusion of identical objects have failed to determine how identical objects projected on strictly peripheral disparate points of the retinas can affect the relative position of the two eyes. The apparatus which he used for his investigation was such that any desired areas of the two retinas could be stimulated with identical stimuli, the relative size, shape and brightness of which could be controlled. As a result of his experiments, Burian believed that powerful visual stimuli are exerted by the peripheral retinal areas, that these stimuli affect the relative position of the eyes and that under certain circumstances they may even cause loss of central fusion. Theoretically, the peripheral portions of the retinas play an important part in the process of fusion. Furthermore, on the basis of his experimental investigations and clinical experience, the author feels warranted in assuming that there are persons with relative asymmetry of the images of the two eyes, that such persons will never be able to fuse simultaneously central and peripheral images and that, therefore, conflicting innervations and considerable discomfort must arise unless the patient is able to suppress either the peripheral or the central part of the images.

SPAETH, Philadelphia.

GLUTAMIC ACID IN MALIGNANT TUMORS. SAMUEL GRAFF, J. Biol. Chem. **130**: 13, 1939.

It has become amply clear in the past few years that all amino acids occurring in proteins have the same "natural" steric configuration, and that all proteins on hydrolysis yield only the levorotatory amino acids. In a recent article on the etiology of malignant tumors Kögl and Erxleben reported the presence of "unnatural," dextrorotatory amino acids, notably glutamic acid, in the products of hydrolysis of malignant tumors. Graff, however, was unable to confirm the findings of Kögl and Erxleben. In a series of 6 malignant tumors he has found only levorotatory (+) — glutamic acid.

PAGE, Indianapolis.

CONVERSION BY THE HUMAN OF THE TESTIS HORMONE, TESTOSTERONE, INTO THE URINARY ANDROGEN, ANDROSTERONE. R. I. DORFMAN, J. W. COOK and J. B. HAMILTON, J. Biol. Chem. **130**:285, 1939.

It has been demonstrated by Dorfman, Cook and Hamilton that testosterone, administered either intramuscularly or orally to men with deficient testicular secretion, can be converted to and excreted in the urine as androsterone. Since androsterone is one of the principal androgens which has been isolated from the urine of men, this conversion of testosterone is interpreted as indirect evidence that in man testosterone may be the testis hormone. The possible intermediates in the conversion of testosterone to androsterone are discussed.

PAGE, Indianapolis.

A STUDY OF NERVE-MUSCLE SPECIFICITY IN THE FORELIMB OF TRITURUS PYRRHOGASTER. JEAN PIATT, J. Morphol. **65**:155 (July) 1939.

Adult specimens of the salamander Triturus pyrrhogaster were subjected to four types of operation involving amputation of the forelimb, section of motor nerves in the forelimb or division and removal of entire nerves. At the end of one hundred and eighty-three days, when forelimb and nerve regeneration was complete, the animals were killed, and the limbs subjected to operation were studied by means of serial sections. The regenerating nerves of the forelimb did not show rigid nerve-muscle specificity. The regenerated nerve pattern was in general normal, and the general degree of nerve-muscle specificity approached the normal condition. The latter was probably due to the fact that the general nerve pattern itself was approximately normal. The presence of a degenerating peripheral nerve trunk was not indispensable in producing a normal nerve pattern. There is apparently no inherent attractive force within any muscle which favors a rigid selective reinnervation, or any inherent antagonism which precludes foreign innervation.

WYMAN, Boston.

PHYSICOCHEMICAL MECHANISMS IN CONVULSIVE REACTIVITY. E. A. SPIEGEL and M. SPIEGEL-ADOLF, J. Nerv. & Ment. Dis. **90**:188 (Aug.) 1939.

Modern theory holds that mechanical, thermal, chemical or electrical stimuli excite nerve cells by changing the ion concentration on the semipermeable surface films of the cells. If the density of these films is lowered, ion concentration is facilitated and the excitability of the cell is increased, unless the cell membrane is so severly injured that changes in ion concentration are not possible. Consequently, one may study the excitability of the brain by measuring the index of polarization, Δ, a factor which represents the difference between the conductivity at a certain high (K_h) and a certain low (K_l) frequency, expressed as a percentage of the conductivity at the low frequency ($\Delta = \frac{K_h - K_l}{K_l} \times 100$). This index of polarization does not depend directly on the conductivity of the brain, and may vary in an opposite direction. The index increases with the density of the semipermeable cell membranes and diminishes as cell excitability is raised. Spiegel and Spiegel-Adolf

have used the index of polarization for investigation of the effects of various convulsive agents on cats and rabbits, and occasionally on the human subject. Measurements were taken directly from the cortex or subcortex of the brain.

The authors report that asphyxia (anoxemia with or without retention of carbon dioxide) lowers the index of polarization both in and beneath the cortex. The process is reversible, the index rising again when oxygen is readministered. The changes in conductivity are more irregular than those in the index of polarization, because the former are affected by the accumulation of such electrolytes as lactic acid and by changes in circulation. Cerebral anemia, induced by ligating the vertebral and clamping the carotid arteries, results in a marked fall in conductivity, due to stoppage of the circulation. The index of polarization also falls at first, but rises thereafter during the vascular occlusion, probably because of coagulation necrosis of many cells. Mechanical increase of intracranial pressure causes a fall of both the conductivity and the polarization index, indicating an increase of excitability. Hyperventilation does the same, since it leads to alkalosis. The index is lowered only slightly by artificial acidosis. Anesthetics and hypnotics tend to increase the index, indicating an increase in density of the cell membranes and a decrease in excitability. Spiegel and Spiegel-Adolf state that epileptogenous agents may act by either or both of two mechanisms: They may change the ion concentration on the surface of the cell and so produce excitation and a convulsion, or they may diminish the density of the cellular membranes and so increase cell permeability, with the result that metabolic or other stimuli become effective and lead to convulsion.

MACKAY, Chicago.

THROMBOKINASE FROM THE BRAIN. J. B. LEATHES and J. MELLANBY, J. Physiol. **96**:38, 1939. THE ACTION OF LECITHINE ON THE THROMBOKINASE OF DABOIA VENOM AND OF BRAIN EXTRACTS. J. B. LEATHES and J. MELLANBY, ibid. **96**:39, 1939.

Leathes and Mellanby prepared thrombokinase from a watery extract of lipoid-free brain tissue by precipitation at p_H 5.5. This substance had approximately the same degree of activity as daboia venom. The thromboplastic activity was increased by the addition of lecithin, especially that obtained from brain tissue. Brain lecithin, in contrast to lecithin obtained from egg yolk, exhibited some degree of thromboplastic activity when used alone. The authors point out that brain tissue contains approximately an optimum amount of lecithin for activation of the thrombokinase present.

THOMAS, Philadelphia.

FURTHER OBSERVATIONS ON MUSCULAR RIGIDITIES IN CATS. E. G. T. LIDDELL and C. G. PHILLIPS, J. Physiol. **96**:39 P, 1939.

Using Adrian electrodes in a Souttar-Beattie stereotaxic apparatus, electrolytic lesions were placed unilaterally in various parts of the basal ganglia (caudate and lenticular nuclei and subthalamic region) of 23 cats. The animals were allowed to survive for periods ranging from one week to four months. No rigidity was evident in the gait after these lesions, unless the destruction was extensive. But when the cat was nursed comfortably on the observer's lap marked "non-clasp-knife" extensor rigidity was evident in the contralateral hindlimb. The head could be rotated and turned toward the side of the lesion. The contralateral, and sometimes also the ipsilateral, eyelids were held immovably open, the nictitating membrane being used spontaneously, or reflexly when the cornea was touched. In walking the animal circled toward the side of the lesion. There were no signs of tremor or of other involuntary movements, even after bilateral lesions.

THOMAS, Philadelphia.

PHYSIOLOGY OF THE MIDBRAIN. R. THAUER and G. PETERS, Arch. f. d. ges. Physiol. **242**:54, 1939.

Thauer and Peters studied the mechanism of decerebrate rigidity in rabbits. Transection of the brain stem was performed in several stages, and the animals

were kept alive up to six and a half weeks after complete transection behind the diencephalon. In some of the animals decerebrate rigidity developed after operation, while in others an increase of extensor tonus failed to appear and the body-righting reflexes remained normal. If rigidity developed, it did not disappear; in 1 case it lasted twenty-three days. In the cases in which decerebrate rigidity was observed, section of the pyramidal tracts was combined with complete or partial destruction of the red nuclei. Such a combination of lesions, however, does not regularly produce rigidity and loss of the body-righting reflexes. In a rabbit that survived operation for thirty days rigidity failed to develop, and the righting reflexes were normal, although the red nuclei were completely destroyed and the rubrospinal and pyramidal tracts were degenerated. This may perhaps be due to the gradual development of destruction of the red nuclei, which allowed adaptation of the remaining parts of the central nervous system to the new situation. Section of the pyramidal tracts in rabbits is followed by a fanning phenomenon (spreading of the toes on stroking the planta of the hindpaw).

SPIEGEL, Philadelphia.

EFFECT OF DECEREBRATION BY PRODUCTION OF ANEMIA ON MOVEMENTS AND TONUS OF THE RESPIRATORY MUSCLES OF THE CAT. M. MONNIER, Arch. f. d. ges. Physiol. **242**:168, 1939.

Sixteen cats were decerebrated by ligature of the carotid and basilar arteries. The resulting decerebrate rigidity was associated with changes of respiration. Ten cats showed a transient, nonspecific change of respiration (slowing, usually with increase of amplitude); in 2 animals the frequency of respiration was definitely decreased, with deep, prolonged inspirations (inspiratory hypertonia); in 4 animals apneic symptoms were observed during inspiration caused by spasm of the inspiratory muscles (diaphragm, external intercostal muscles). These specific effects on respiration may be increased by vagotomy, but section of the vagus nerves is not a prerequisite for their development. It is assumed that the inspiratory muscles react on loss of rubrospinal inhibition with increase of tonus in a way similar to that of the extensor muscles of the extremities. Faradic stimulation of the substantia reticularis ventralis of the medulla oblongata produces spasm of the inspiratory muscles. The respiratory changes produced by decerebration are therefore probably due to release from this region.

SPIEGEL, Philadelphia.

Neuropathology

PRIMARY FIBROSARCOMA OF THE BRAIN. LILLIAN COTTRELL, Arch. Path. **27**:895 (May) 1939.

Up to the present only 6 tumors composed of fibroblastic tissue have been reported as primary in the brain substance. Histologically they have resembled fibroblastoma occurring elsewhere in the body, although their origin in the brain has been a moot question. Cottrell reports the seventh case of such a tumor, occurring in a white man aged 52 who showed mental symptoms for five years. There gradually developed hemiparesis, "stumble in speech" and an occasional convulsion. Exploration failed to reveal a tumor in the left frontal region. At autopsy two fibroblastic tumors were observed, one near the left frontal pole and the other in the left temporal lobe. These were considered by the author to have origin from the adventitia or its precursor, the less differentiated mesenchymal cells. The tumors were classed as sarcomas because of their invasive properties and because of the evidence of rapid growth.

WINKELMAN, Philadelphia.

METASTATIC MELANOBLASTOMAS OF THE BRAIN. C. B. COURVILLE and ROBERT J. SCHILLINGER, Bull. Los Angeles Neurol. Soc. **4**:8 (March) 1939.

Courville and Schillinger report 18 cases of metastatic melanoblastoma of the brain. They found that these represented 13 per cent of all metastatic intra-

cranial tumors and 1.3 per cent of tumors of the brain in general. Figures in the literature indicate that 50 per cent of melanoblastomas metastasize to the brain. In the cases reported by Courville and Schillinger the age limits were 24 and 80 years. Ten of the 18 patients were men. The primary lesion was in the skin in 9 cases and in the viscera in 4 cases, and the site was unknown in 5 cases. The metastatic nodules tend to occur predominantly in the cortex or in the central gray nuclei, possibly as a result of the rich blood supply to these regions. There may be numerous small nodules scattered widely through the brain, a few large and small nodules or extensive tumor masses in the brain. Sometimes the nodules are colorless or gray instead of black. Smaller nodules tend to be seen about the sylvian fissure, and generally in the area supplied by the middle cerebral artery. The large tumor masses are frequently surrounded by extensive areas of softening, so that the tumors may be easily removed surgically or may easily break away and form secondary implantations in the subarachnoid spaces of the base of the brain and the lower part of the spinal cord.

MACKAY, Chicago.

FAMILIAL DIFFUSE SCLEROSIS (PELIZAEUS-MERZBACHER DISEASE). KARL O. VON HAGEN and C. W. SULT JR., Bull. Los Angeles Neurol. Soc. **4**:23 (March) 1939.

Von Hagen and Sult report 2 cases of Pelizaeus-Merzbacher disease in brothers, with a pathologic description of 1 of them. A boy, aged 9 when examined, had had a normal birth and development until he was 4½ years old. At that time he began to walk stiffly on his toes. Spastic paraplegia progressed steadily; in two years he was bedfast. Speech was gradually lost. Examination showed extreme spastic paraplegia, widespread athetotic movements and frequent extensor spasms with upward deviation of the eyes. Optic atrophy was present bilaterally, and the plantar responses were pathologic. Hearing was preserved, and there were no gross sensory disturbances. There was marked mental defect. Laboratory studies, including the Wassermann test of the blood, gave negative results.

Pathologically, there was widespread demyelination of the white matter except for the arcuate fibers and some islands of preserved myelin. The areas of demyelination were essentially in the form of perivascular rings. The white matter of the cerebellum was similarly involved, while the basal ganglia, dentate nuclei, cerebellar peduncles and medullary nuclei were well preserved. The cells of the cortex were normal, but the projection fibers were largely demyelinated. There were descending degeneration of the pyramidal tracts and incomplete demyelination of the extrapyramidal tracts and the ground bundles in the cord. Some astrocytic gliosis was present, but the glia was undergoing degeneration with loss of processes and formation of "ameboid glia."

The patient's brother was normal until the age of 3½ years, when he began to lose his speech. Movements became awkward and the patient apathetic. The pupils did not react to light; the tendon reflexes were increased, and Babinski and Oppenheim reactions were present on the left. Sensation was normal. Von Hagen and Sult believe that the process began in the white matter of the cerebrum and cerebellum, with secondary degeneration in the spinal cord. The involvement of the extrapyramidal and ground bundle pathways in the cord must, however, have been primary.

MACKAY, Chicago.

TWO AUTOPSIED CASES OF ANOSOGNOSIA. KARL O. VON HAGEN and ELINOR R. IVES, Bull. Los Angeles Neurol. Soc. **4**:41 (March) 1939.

Von Hagen and Ives record 2 cases of anosognosia (unawareness of hemiplegia) in which the lesion, contrary to the usual conception, was not located in the right thalamus, but only in its immediate vicinity. In the first case a woman was totally unaware of her left hemiplegia and denied its existence. There were considerable mental impairment, left homonymous hemianopia and reduced sensi-

bility, as well as paralysis of the left side of the body. Conjugate gaze to the left was weak. Autopsy revealed a hemorrhage destroying the entire right corpus striatum, but leaving the thalamus grossly and microscopically intact. In the second case a man denied his left hemiplegia, which was associated with some clouding of consciousness, impaired sensibility on the left side of the body, conjugate deviation of the eyes to the right and diminution of the attention to objects in the left visual field. Autopsy disclosed softening and edema of the right parietal and portions of the right temporal lobe, but no disturbance of the thalamus. Von Hagen and Ives conclude that anosognosia may result from isolation of the thalamus of the minor hemisphere from the cortex.

MACKAY, Chicago.

A CASE OF ACUTE HEMORRHAGIC POLIOENCEPHALITIS SUPERIOR (WERNICKE) WITH AUTOPSY. J. M. NIELSEN and M. MONICA MILLITZER, Bull. Los Angeles Neurol. Soc. **4**:82 (June) 1939.

Neilsen and Millitzer describe the case of a woman aged 52 who had been addicted to alcohol for many years. She was hospitalized because of convulsions and proved to have a confabulatory psychosis and almost complete paralysis of all extraocular movements. The pupils were sluggish, and there was constriction of the upper fields of vision, with slight weakness of the right side of the face. Peripheral neuritis was evidenced by weakness, areflexia and sensory impairment, but there was no pain or tenderness of the extremities. The spinal fluid was normal except for the presence of 100 mg. of total protein per hundred cubic centimeters. The Wassermann reaction of the spinal fluid was negative; that of the blood was positive. The patient died of bronchopneumonia sixteen days after admission. Multiple small hemorrhages, both old and recent, were observed in both thalami and in the midbrain below the aqueduct. There was proliferation of the walls of the blood vessels, not only in these regions but also in the cerebral cortex. The leptomeninges showed chronic thickening.

MACKAY, Chicago.

DIFFERENTIAL DIAGNOSIS BETWEEN TUMOR OF THE BRAIN AND MENINGITIS BASED ON THE SPINAL FLUID FINDINGS. F. UTZ, Deutsche Ztschr. f. Nervenh. **148**:187, 1939.

Utz emphasizes the importance of examining the sugar content of the spinal fluid in cases in which the differential diagnosis between tumor of the brain and meningitis is doubtful. He reports the case of a patient who showed signs of diffuse involvement of the brain. The spinal fluid had a total protein content of 125 mg. per hundred cubic centimeters and 300 lymphocytes per cubic millimeter. The sugar was reduced to 7.8 mg. per hundred cubic centimeters. The spinal fluid pressure was increased. The chloride content was not determined. The diagnosis of tumor of the brain and tuberculous meningitis was regarded as possible from the findings. At necropsy tuberculous meningitis and intracerebral tuberculomas were observed.

ADLER, Boston.

THE GLOBUS PALLIDUS IN ATHETOSIS AND PARABALLISMUS. K. BALTHASAR, Deutsche Ztschr. f. Nervenh. **149**:243, 1939.

Balthasar reports 2 cases of extrapyramidal disease, with observations at autopsy. The first patient, aged 28 years, had suffered from bilateral athetoses, abasia and astasia since a few days after birth. She was an idiot. In later life she showed involuntary movements, together with extension spasm of the back. At autopsy the pallidum was seen to be reduced in size bilaterally. Histologically, there was status marmoratus in the dorsolateral portion of both putamens and status dysmyelinatus in the pallidum. The number of ganglion cells was reduced, associated with an increase in glia cells within the pallidum. Balthasar assumes that the damage to the putamen and to the pallidum occurred at the same time.

The second patient, a woman aged 66, suffered from paraballismus and died two months after its onset. She had spells of involuntary laughing. She started with ballistic movements of her left arm and leg, followed a few weeks later by similar movements of the right side. The facial muscles showed continuous involuntary movements. There were no abnormal reflexes of the arms and legs. Astasia and abasia were marked, and the muscles were hypotonic during periods of rest. Occasionally revolving around the body axis was observed. At autopsy generalized arteriosclerosis was observed. The striatum and pallidum were reduced in size bilaterally. There was a large area of softening in the left pallidum, with gitter cells, proliferation of glia and perivascular lymphocytic infiltrations. Perivascular infiltrations of the same type were observed within the internal capsule. The nerve cells were rarefied in the putamen and, to a lesser extent, in the caudate nuclei. There was no hemorrhage in the corpus Luysi, but rarefaction of myelin fibers and nerve cells, together with proliferation of glia, was present. The substantia nigra was intact. All the damage was bilateral, with moderate and varying differences in the degree of involvement. Balthasar supports the belief that the hyperkinesis was caused by the recent softening in the pallidum, since the damage of the corpus Luysi was histologically of long duration.

ADLER, Boston.

PATHOLOGIC PICTURE AND PATHOGENESIS OF MEDULLOBLASTOMA. I. SCHEINKER, Monatschr. f. Psychiat. u. Neurol. **101**:103 (May) 1939.

Scheinker reports a case of cerebellar tumor in a patient aged 49. The symptoms began after a fall, suggesting that trauma may have acted as a precipitating factor. The pathologic picture conformed to that of medulloblastoma. The tumor, located in the lateral and superior portions of the vermis, was an infiltrating growth, consisting of undifferentiated round or oval cells in a delicate reticulum. The nuclei were rich in chromatin, and most of the cells contained little cytoplasm. Apart from the tumor, the surface of the cerebellum was covered in many places by several layers of cells, which unquestionably represented a persisting embryonal external granular layer, the so-called Obersteiner layer. It is believed that the tumor arose from proliferation of these cells, since they were morphologically similar to those of the tumor, and serial sections disclosed a point at which they extended directly into the new growth. This observation confirms Marburg's theory that medulloblastoma belongs to the group of tumors which originate from embryonal malformations.

ROTHSCHILD, Foxborough, Mass.

POSTVACCINAL ENCEPHALOMYELITIS. B. BROUWER, Maandschr. v. kindergeneesk. **8**:379 (July) 1939.

Brouwer demonstrates that the incidence of postvaccinal encephalomyelitis is decreasing in the Netherlands because the frequency of vaccination has decreased. In 1938 3 cases of encephalomyelitis were accepted by the Governmental Committe for Encephalitis as postvaccinal in origin. Two of these were studied microscopically. Typical areas of demyelination with perivascular increase of microglia cells were seen scattered through the entire central nervous system. These histologic changes are a constant manifestation in the postvaccinal form of encephalomyelitis, but they do not exclude other forms, because they can be observed also in other postinfectious encephalitides. The author emphasizes that the formerly widely accepted belief that patients with postvaccinal encephalitis either succumb or recover without residual defects is not correct in that cases have been observed in which tetraplegia or other forms of invalidism persisted many years later. As regards the pathogenesis, the author does not accept the theory of activation of a virus already present in the central nervous system before vaccination. He believes that the encephalitis is caused by the vaccinia virus itself, but that an endogenous factor is to be considered.

J. A. M. A.

Psychiatry and Psychopathology

LOSS OF RECENTLY ACQUIRED LEARNING DUE TO METRAZOL THERAPY. EUGENE ZISKIND and ESTHER SOMERFELD-ZISKIND, Bull. Los Angeles Neurol. Soc. **4**:77 (June) 1939.

Ziskind and Somerfeld-Ziskind report the case of a man aged 40 who apparently recovered completely from a paranoid schizophrenic psychosis of one month's duration after receiving sixty-two insulin shocks. After three months of normal life he again experienced paranoid ideas in brief flashes, associated with insight. Convulsions were then induced with metrazol; after twelve such convulsions the patient again lost his delusions, but showed a persistent memory defect for recently acquired skills. He forgot how to play "Chinese checkers" and how to keep score in badminton, both recently learned. He failed to recognize a restaurant and a sports store he had been in once previously. Memories for more remote events were not disturbed. In another patient, Ziskind and Somerfeld-Ziskind noted a persistent memory defect, with features of an organic psychotic syndrome, following injections of metrazol. They add that "most of the other patients receiving the same drug showed transient memory defects for recent events." They believe that the injury produced in the brain by metrazol, probably as a result of anoxia, seems to destroy recently acquired impressions first, leaving earlier patterns intact. They suppose that perhaps a recently acquired psychosis may be destroyed in the same way.

MACKAY, Chicago.

UNCONSCIOUS PHANTOMS IN NEUROTICS. FRITZ WITTELS, Psychoanalyt. Quart. **8**:141, 1939.

Wittels points out that there are two ways in which the mechanism of identification may be used. If one admires a great man, the correct way to identify oneself with him is to acquire the values for which he is admired and to continue his work. This may take many years of hard work, with the possibility of failure because of inefficiency. Another way, which is partial and unconscious, is to identify oneself with some mannerism of the great man. The result is the development in one's personality of a fantom part of the great man.

The neurotic person may show a number of such individual fantoms; some of these he must live up to, some he fears and some he hates or secretly loves. Often one fantom is incompatible with another, and this incompatibility forces him into conflicts.

From this point of view, Wittels reports a case of a compulsion neurosis and one of hysteria. In the case of compulsion neurosis there were at least five fantoms: one which represented the grandmother and was very puritanical; one which represented a defeated, ugly girl; one a voluptuous beauty; one an honest man who depended solely on his own mind, and one an orderly, impeccable wife and mother. The conflict of these various fantoms is evident. The patient reacted to the fantoms and solved the conflict between them by defending herself against them by a rigid system of righteousness. In the case of hysteria there was a fantom of a saint, a virgin, a prostitute, a "pal" with boys and several others. The patient attempted to deal with them by acting out their various characteristics until she became caught in the web of her very complicated actions. Wittels points out that an important phase of psychotherapy is to have the patient see and understand the fantoms by which he is vexed.

PEARSON, Philadelphia.

ON CERTAIN PROBLEMS OF FEMALE SEXUAL DEVELOPMENT. KURT EISSLER, Psychoanalyt. Quart. **8**:191, 1939.

Infant female sexual development consists first in turning away from the mother, the formation of a passive, libidinal attachment to the father and shifting of the cathexes and sensitivity from the clitoris to the vagina. Freud stated that when the girl turns to her father the love emotions are directed to him, while the

hatred remains attached to the mother with the appearance of emotions, i. e., penis envy and the castration complex, which change her fantasies from an active to a passive character. Boys would acquire a castration complex even if they had never seen the female genitals, but apparently girls do not acquire such a complex without having observed the male genitals. The boy has real psychic and physical grounds for his fear of castration.

The girl's fantasy that her mother has deprived her of a penis has no real psychic or physical grounds, and so forms the first instance of a fantasy with no justification in reality that is not only useful but necessary in the development of a group of human beings. However, if the girl discovers close to the clitoris a hollow organ, her conception of a quantitative difference between the sexes becomes transformed into a qualitative one, and as she recognizes that both she and her mother are different from her father, she realizes that neither actively or passively would she obtain from her mother her wish for an organ of penetration.

The knowledge of the vagina may be rejected or the sensations may be interpreted as coming from some other part because it is located between two erogenous zones (the clitoris and the anus) both of which have a pleasurable and a self-preservative function. The vagina lacks the latter function, and by the time the vagina raises its claims the ego has attained a fairly advanced state of organization and has many defense mechanisms at its disposal to avoid recognition of the instinctual urge.

The greater ambivalence shown by girls may be the result of the simultaneous occurrence of active clitoridian and passive vaginal impulses. The girl's regressive turn to masochism may be the masochistic elaboration of an instinct with strongly passive aims, or it may be that the basic forces in vaginal impulses have no self-preservative function, or that they cause the girl's tendency to incorporate her father in an oral way. The hallucination of a desired penis is a reaction formation against the vaginal instincts.

The vaginal instinct suffers another dysfunction. The physiologic history of the vaginal mucous membrane up to the onset of menstruation is not uniform, but there are changes in the acid-base reactions of the vaginal secretion due to hormone action which facilitate or hinder the growth of bacteria. Bacterial infection is responsible for mild pathologic changes, which are often indicated clinically by leukorrhea.

Vaginal masturbation is not uncommon in little girls, but is not as common as the clitoral form, because if the parents are at all strict it is difficult to perform. The use of foreign objects for vaginal masturbation may arise spontaneously in the child or may be the result of seduction by some one else. Its spontaneous occurrence is the result of a desire to use the vagina as a mouth and to incorporate objects in it.

The evidence seems to indicate that the girl may discover her vagina spontaneously before puberty and may strive to gain autoerotic satisfaction from it. Outside influences, inner inhibitions or hereditary constitutions may prevent this discovery. Certainly, outside influences are more effective in preventing vaginal than clitoridian masturbation. The fact that the vagina may be discovered before puberty or sexual intercourse, even if seduction has not occurred or an anomalous constitution does not exist, indicates that such discovery and its result must be included in any scheme of female sexual development.

PEARSON, Philadelphia.

AGGRESSION IN EARLY CHILDHOOD. KARIN STEPHEN, Brit. J. M. Psychol. **18**:178, 1939.

Stephen believes that aggression is first called forth in inner anxiety situations in infancy which seem to threaten the ego. If the frustration causing the anxiety is too great, whether inner or outer or mixed, it may be experienced as intolerable ego danger and handled by flight, projection, introjection or repression. Secondarily, these do not relieve the anxiety, and a vicious cycle is set up, with useless displays of aggression. When this mechanism is carried to adult life, it defeats

healthy living. Stephen believes, however, that aggression is necessary to normal development and if properly used is valuable in helping the person to integrate properly with society.

ALLEN, Philadelphia.

PSEUDOTABETIC AND PSEUDOPARALYTIC PICTURES IN CONCUSSION PSYCHOSES. P. EICHLER, Arch. f. Psychiat. **109**:282 (Jan.) 1939.

In 3 cases of atypical psychoses due to concussion, clinical features of pseudotabes were observed. In 2 of these there were, in addition, maniclike disturbances in mood and confabulatory, grandiose delusions which were similar to some of the psychotic features observed in dementia paralytica. There were no indications of predisposing, endogenous or exogenous etiologic factors of any kind, particularly no history of alcoholism. The development of the psychotic features and other specific symptoms of involvement of the brain depended entirely on the type, extent and localization of the lesion. The pupillary reflexes were not like those of tabes, for instead of absence of the light reflex alone, combined with miosis, there were involvement of the convergence reflex and vacillation in the size of the pupil. The disturbance, furthermore, did not coincide with that of Adie's syndrome. The decrease and absence of reflexes were not purely transitory; in one case they had lasted for several years. There was a combination of hypotonia and areflexia.

It is somewhat problematic exactly how to explain the development of the grandiose and manic features. It is possible that these may be related to the lesions of the midbrain and diencephalon with hypothalamic involvement. The neurologic symptoms point in this direction, and the Korsakoff-like mental picture has occasionally been found in diencephalic disturbances. However, the present cases cannot be regarded as either proving or disproving this contention.

W. MALAMUD, Worcester, Mass.

PATHOPHYSIOLOGIC CHANGES IN PERIODIC CATATONIC STATES. R. GJESSING, Arch. f. Psychiat. **109**:525 (Feb.) 1939.

Gjessing states that the characteristic changes in the blood chemistry in catatonia are disturbances of nitrogen balance. He finds that either at the beginning or at the end of a negative nitrogen balance there is development of the "reactive phase," consisting of excitement or stupor. In patients in whom this occurs at the onset of the negative nitrogen balance there is during the free interval a retention syndrome, characterized by nitrogen retention, low basal metabolism and vagotonic symptoms. During the reaction phase there is a compensation syndrome, with increased elimination of nitrogen, high basal metabolism and sympathicotonic symptoms. In cases in which the reaction phase occurs after several weeks of negative nitrogen balance the basal metabolism is also low in the free interval and increased during the active phase, but the nitrogen elimination is increased during the free stage and decreased during the excitement. During the active phase one can generally distinguish three forms of reactions: (1) those due mainly to the excitement (psychomotor features and changes in basal metabolism, pulse frequency and blood pressure); (2) those due to both clinical features and the peculiarities of nitrogen balance, such as diuresis and changes in acid-base equilibrium, and (3) the fundamental symptom, the vacillations in the nitrogen balance.

Compensation for the disturbances both in mental and in somatic function develops principally after increased nitrogen elimination is obtained through administration of thyroxin. In some of the cases one can decrease the amount of thyroid medication after several months of administration and in time may actually stop it without the development of nitrogen retention again. In other cases it is necessary to continue thyroid medication for years. In these cases cessation of the treatment leads to renewed attacks of either excitement or stupor. The author emphasizes that patients with this form of recurrent catatonic attacks can be kept symptom free only on the basis of this treatment. They cannot, however, be considered cured.

MALAMUD, Worcester, Mass.

Diseases of the Brain

ANTERIOR PITUITARY TUMOR ASSOCIATED WITH CACHEXIA, HYPOGLYCEMIA, AND DUODENAL ULCER. MAURICE P. FOLEY, ALBERT M. SNELL and WINCHELL M. CRAIG, Am. J. M. Sc. **198**:1 (July) 1939.

Foley, Snell and Craig report the case of a Jewish man aged 28 whose illness began in 1933 with symptoms suggestive of a duodenal ulcer, but which was not diagnosed until 1934. His weight had dropped from 178 to 140 pounds (80.7 to 63.5 Kg.) between September and December 1934, when he was admitted to the hospital. Laboratory studies revealed: blood sugar, 43 mg.; urea, 20 mg., and chlorides, 487 mg. per hundred cubic centimeters. The highest value for blood sugar obtained at any time during the thirty-one days the patient stayed in the hospital was 78 mg., the lowest 30 mg. The general habitus was eunuchoid, with loss of weight and weakness. Basal metabolic rates obtained on two occasions were minus 23 and minus 22 per cent, respectively. A roentgenogram of the head revealed enlargement of the sella turcica, grade 4, with thinning of the posterior clinoid processes. Accurate perimetric methods revealed bitemporal hemianopia for small objects and for color. To improve the patient's general condition before operation anterior pituitary extract was used, with negative results, and extract of adrenal cortex had no effect. On the fifteenth day after admission right transfrontal craniotomy was performed for removal of the pituitary tumor; a large, cystic, degenerating adenoma was exposed, which proved to be chromophobic. Because of the infiltration of the tumor into the adjacent structures only a portion was removed. The patient received high voltage therapy for five days over the region of the tumor. He died about two months after dismissal, death presumably occurring from exhaustion and cachexia. It seemed probable that all the patient's symptoms were secondary to the presence of the original neoplasm and were in general referable to the destruction of the anterior lobe and suppression of its hormonal activity.

MICHAELS, Boston.

SYMPTOMATOLOGY OF TUMORS OF THE THIRD VENTRICLE. J. M. NIELSEN and R. B. RANEY, Bull. Los Angeles Neurol. Soc. **4**:1 (March) 1939.

Nielsen and Raney report 2 cases of tumor in the third ventricle to emphasize the importance of amnesia for recent events and changes in emotion and personality in establishing the diagnosis. In the first case a man aged 44 rapidly lost memory for recent events, until he could not recognize a motion picture on the second of two successive presentations. He prolonged his vacation indefinitely because he continued to think it was just beginning. In addition, there were apathy, somnolence and polydipsia, with loss of judgment in financial matters and, later, unreasonable outbursts of temper. Examination revealed questionable papilledema, feeble pathologic reflexes and a low basal metabolic rate (minus 38 per cent). Ventriculographic examination at first gave doubtful results but three years later confirmed the diagnosis of tumor in the third ventricle. Eight hours after removal of a cystic tumor the patient died with hyperthermia. In the second case a man aged 30 presented marked disorientation and confusion due to amnesia for recent events. He was apathetic, somnolent and incontinent, and had slow, thick speech. The pupils did not respond to light; the disks were choked, and pathologic reflexes were present bilaterally. A ventriculogram confirmed the diagnosis of tumor in the third ventricle. The tumor was removed successfully, but the patient died of pneumonia on the twelfth postoperative day.

MACKAY, Chicago.

CURRENT CONCEPTIONS IN EPILEPSY. M. BROWN, Illinois M. J. **76**:132 (Aug.) 1939.

Brown states that it has been clearly demonstrated that epilepsy and other nervous and mental diseases occur more frequently among the ancestors and collateral relatives of deteriorated persons with epilepsy than among the general

population. The offspring of persons with epilepsy are susceptible to the disease and to defective mental development and other neuropsychiatric disorders. In a study of the hereditary factors in epilepsy in which the records of nondeteriorated epileptic patients were used it was found that the hereditary backgrounds of these patients are tainted with neuropathic disturbances to a significantly less degree than are those of deteriorated patients. Epilepsy occurred in only 1 of 342 children born to 163 extramural patients with the same disorder. Infantile convulsions occurred in 6 of these children. The deteriorated and nondeteriorated patients with epilepsy, it appears, show a distinct and significant difference in the relation of hereditary factors to their disorder. There are constitutional or inborn differences between mentally deteriorated and nondeteriorated epileptic patients. Not only are there important clinical differences between the mentally normal person with epileptic seizures and the psychotic patient with epilepsy, but the differences in hereditary background and in native or constitutional makeup suggest the existence of a fundamental distinction between these two groups of patients.

J. A. M. A.

Intracranial Chondroma. M. I. Green and J. H. Childrey, J. Nerv. & Ment. Dis. **89**:650 (May) 1939.

Green and Childrey report the case of a man aged 44 who at the ages of 20 and 29 had had attacks of sharp pain with temporary blindness in the right eye. For the past four years there had been intermittent diplopia, and for two weeks, acute pains in the right eye, followed by ocular protrusion and ptosis. Examination revealed complete ptosis of the right upper lid, slight miosis, absence of all pupillary reactions, moderate protrusion and some outward rotation of the eye. The fundus was normal, but there was a small central scotoma, which had reduced vision to 10/30. After removal of a biopsy specimen from a slight swelling in the nasopharynx, the patient experienced severe pain on the right side of the head and left hemiplegia. He died four days later. Autopsy revealed a soft tumor, measuring 5 by 3 by 3 cm., arising from the region of the right occipitotemporal suture and invading the middle fossa beneath the dura. It impinged on the third, fourth, fifth and sixth cranial nerves, displacing the cavernous sinus upward, the gasserian ganglion forward, the jugular vein posteriorly and the internal carotid artery laterally. The mass had been swollen by a recent hemorrhage and had compressed the right side of the pons. Hemorrhage had occurred into the right optic nerve behind the eyeball. Microscopically, the tumor consisted of solid sheets of small round nuclei arranged irregularly in a mass of chondromucin, separated by strands of fibrous tissue. There were no evidences of malignancy.

Mackay, Chicago.

Tumor of the Corpus Callosum. J. A. Barré, Kabaker, Pernot and Ledoux, Rev. neurol. **71**:389, 1939.

Tumors of the corpus callosum are rare; they constitute only 0.6 per cent of the 2,000 intracranial tumors reported by Cushing. The case reported here was that of a man aged 38 who for about one year had shown bizarre behavior and forgetfulness. In the two months before study marked aggravation of this condition occurred. Speech and answers to questions became slow. There were vague headaches. One month before admission a diagnosis of psychasthenia with depression was made by another physician. In the last two weeks the apathy increased, the patient became indifferent to his surroundings and incontinence of urine and feces appeared. He lay in bed motionless. When he was spoken to he answered after a variable delay, or did not reply at all. He could be roused by asking energetically: "Do you not wish to answer me?" He would then jump as if he had been asleep and assure his questioner that he wanted to answer, but a few minutes later he would lapse once more into inaccessibility. When food was brought he did not touch it, yet allowed himself to be fed by the nurse, chewed carefully and ate a great deal. When he received a letter and was urged

to read it, he opened the envelope and placed the letter on the table, but made no attempt to read it. There was a tendency to facetiousness and euphoria. The patient was unconcerned about his illness. He was disoriented for space and had false recognition. There was no dysarthria, alexia, aphasia or apraxia. Walking was characterized by a tendency to deviate to the left and backward. There were a slight tremor of the hands and slight weakness of the right side of the face. The remainder of the neurologic examination gave normal results. There was no papilledema or other sign of intracranial hypertension. Examination of the spinal fluid did not reveal any pathologic features. Lumbar pneumographic examination, with 15 cc. of air, revealed lack of filling of the right lateral ventricle and dilatation of the left ventricle in a face view, with the patient standing. The lateral view showed slight filling of the posterior horns. With the patient lying with his forehead on the plate there was slight filling of the left posterior horn. With the occiput on the plate there was no air in either ventricle. On the day after the spinal tap the torpor increased. The following day the patient passed into coma, vomited and hiccuped. The temperature rose to 40 C. (104 F.); the pulse became slow; respiration was stertorous, and there was intense sweating. The patient died. The brain was tense, with flattened gyri. There was engagement of the temporal lobe bilaterally. A large tumor occupied the entire corpus callosum and infiltrated the centrum ovale of each hemisphere, following the direction of the callosal radiations. The left side was more involved than the right. The internal frontal and the fornicate gyri were invaded on the left. The callosal radiations in the occipital region were not involved. The septum pellucidum and the neighboring portion of the fornix were invaded. There was a recent hemorrhage into the tumor and into the lateral ventricles. The tumor was a glioma, with small cells. The clinical syndrome in this case recalls that described by Guillain and Garcin, by Alpers and Grant and by Alpers. In particular, the imperviousness to stimuli of all sorts, described by Alpers, was a striking feature. Guillain and Garcin found signs of intracranial hypertension less marked than with other tumors. In the case reported the disturbances of equilibration could be temporarily corrected by urging the patient to do so. The impairment of attention which characterizes callosal tumors is the probable mechanism of the disequilibrium, which should not be called ataxia.

LIBER, New York.

PSYCHIC DISTURBANCES ACCOMPANYING TUMORS OF THE ORBITAL PART OF THE FRONTAL LOBE. P. DUUS, Arch. f. Psychiat. **109**:596 (Feb.) 1939.

Duus analyzes the character changes in persons with tumors affecting the orbital part of the frontal lobes on the basis of 5 cases of his own and 25 cases collected from the literature. In most of these instances the tumors were bilateral meningiomas. In practically all the cases a characteristic mental syndrome became manifest early in the disease process. The patients were usually middle-aged persons without signs of mental disturbance before the onset of the disease. The process began with childish, superficial behavior, showing a tendency to facetiousness and loss of tact and appreciation of moral values, and minor criminal or delinquent activities. In most cases the mood showed a tendency toward euphoria and grandiosity. In some there was a tendency toward depression, irritability and dissatisfaction. In all cases there was increased activity of instinctive drives, manifesting itself in childish sexual escapades, autoeroticism, alcoholism and the like. Disturbances in memory developed some time after the onset of the character changes. All the mental symptoms came on early in a consistent fashion, before definite organic signs.

With further destruction of the brain tissue, new symptoms developed, such as loss of interest in work and social activities and general deterioration, with neglect of personal habits. In some cases hallucinations developed at this time, with marked poverty of motor and mental activity. At this time, too, the first definite physical symptoms, such as headaches, vomiting and visual disturbances appeared.

At the same time local symptoms, such as choked disks, optic atrophy, disturbances in smell, ptosis, pupillary disturbances, paresis of the facial and hypoglossal nerves and signs of involvement of the pyramidal tracts, were observed. Frequently epileptiform attacks were observed at this time. As a final stage, owing to further increase in size of the tumor, there were manifestations of lesions of the brain stem, such as delirious states, somnolence and stupor.

The author emphasizes that the character changes develop consistently early in the disease and at a time when operative intervention would mean the highest degree of therapeutic success. It is for this reason that in cases in which these changes appear the utmost care should be taken to investigate the existence of a tumor in this region.

MALAMUD, Worcester, Mass.

A LOCAL FORM OF PANENCEPHALOMYELITIS OF THE TYPE OF JAPANESE ENCEPHALITIS. H. PETTE and G. DÖRING, Deutsche Ztschr. f. Nervenh. **149**:7, 1939.

Pette and Döring describe a form of encephalitis, perhaps new to Germany. The disease begins subacutely with restlessness and delirium after more or less definite prodromes (headache, dizziness and confusion). Sometimes pyramidal, sometimes extrapyramidal, symptoms predominate. Hyperkinesias, such as myoclonias, choreiform and athetoid movements and tremors, occur. There is a tendency to bizarre postures. Bulbar symptoms, even anarthria and trismus, are almost constant. Occasionally vegetative disturbances are striking. The spinal fluid may contain up to 30 cells. The course of the disease, beginning with noncharacteristic, mild fever, may extend over a period of from several days to months. The neurologic symptoms may regress. Anatomically, the encephalitic process extends over the entire central nervous system, including the meninges. Certain areas are usually spared, namely, the substantia nigra, red nucleus and pallidum. The inflammatory character of the alterations is shown by the occurrence of infiltration in the meninges and the intracerebral vessels. Lymphocytes, with a few plasma cells, occur. Glial foci (Hortega cells), suggestive of those seen in typhus, are also observed. No transmission experiments were performed.

PUTNAM, New York.

CLINICAL AND PATHOLOGIC MANIFESTATIONS OF "ENCEPHALITIS B" (ST. LOUIS TYPE). T. WERNER, Deutsche Ztschr. f. Nervenh. **149**:66, 1939.

Werner reports a case of acute encephalitis. The history of fatigue, dizziness, headache and convulsions was not striking. There was irregular fever. A Babinski sign was elicited bilaterally, but neurologic examination revealed otherwise nothing remarkable. The protein content of the spinal fluid was increased, and the cell count was 30 per cubic millimeter. The patient died in two days. The histologic changes showed a close relationship to those in cases in the St. Louis epidemic in 1934. Perivascular infiltrations were scattered diffusely throughout the brain, without special affinity for the basal ganglia. Changes in the ganglion cells were observed principally in the cortex and the basal portions of the medulla and pons. The meninges were infiltrated. The region of the corpora quadrigemina was not involved. No areas of destruction and no glial foci were observed. The author considers that the disease in his case belongs to the same group as encephalitis of the St. Louis type and "encephalitis B."

PUTNAM, New York.

A POST-TRAUMATIC SYNDROME OF THE THALAMUS AND EPIPHYSIS. L. BENEDEK and L. ANGYAL, Deutsche Ztschr. f. Nervenh. **149**:196, 1939.

Benedek and Angyal report the case of a patient who had suffered bilateral fracture of the skull. In the course of the disease signs of injury to the right pyramidal tract, opisthotonos and compulsive laughter were observed. Four months later there was still constant conjugate deviation of the eyes to the left, and the patient was unable to move the eyes in any other direction. There were ataxia

and impairment of sensibility on the right side, insomnia, adiposity and increase in intake of fluids to 3 liters daily. Psychomotor attacks occurred during which the patient was observed to rotate about his longitudinal axis several times. There was marked hypersexuality. Pain and swelling of the mammary glands were observed. Most of the signs are explained by the authors on the assumption of an injury to the thalamogeniculate artery, which provides the blood supply for the inferoposterior part of the thalamus. In addition, they assume an injury to the epiphysis because of the change in the mammary glands, while the disturbance in metabolism, sexual abnormality and moderate polydipsia are attributed to an injury to the hypothalamus and infundibulum. The patient survived.

ADLER, Boston.

AFTER-EXAMINATION OF PATIENTS WITH UNCOMPLICATED CONCUSSION OF THE BRAIN, WITH SPECIAL REGARD TO IMPORTANCE OF DURATION OF PRIMARY REST IN BED. S. WITH, Norsk. med. (Hospitalstid.) **3**:2057 (July 8) 1939.

With asserts that brief individualized confinement to bed of patients with uncomplicated concussion of the brain does not seem to give less favorable results either as to the time when the patients are able to resume their full work or as to the number of patients whose injuries are permanent than prolonged rest in bed in corresponding groups, nor is the tendency to grave permanent injuries greater. He reviews the 394 cases (272 of mild, 97 of moderate and 25 of grave concussion) of patients treated in Sundby Hospital from 1924 to 1934 with individualized confinement to bed according to the duration of the symptoms. In 257 cases (65 per cent) the rest in bed was for less than one week, in 95 cases (24 per cent) from one to two weeks, in 31 cases (8 per cent) from two to three weeks, in 8 cases (2 per cent) from three to four weeks, in 3 cases (1 per cent) for four weeks or more. He examined 328 patients (84 per cent) in their homes; 9.6 per cent could not be traced, and 6.4 per cent had died, presumably not of accident. Permanent sequelae were found in 16.1 per cent (severe sequelae in 6 patients, moderately severe in 8, slight in 7 and very slight in 27). The tendency to permanent injury, he says, increases with age. There was no demonstrable connection between the severity of the acute symptoms and the occurrence of permanent sequelae. Work was resumed within one month after discharge by 66 per cent of the patients and within from one to three months by 18 per cent. Less than 1 per cent were permanently disabled. Of 250 persons without permanent injury, 57 per cent were wholly free from symptoms one month after discharge and 73 per cent of all three months after discharge. In the remaining 27 per cent the general postcommotional symptoms disappeared more slowly.

J. A. M. A.

Peripheral and Cranial Nerves

EVALUATION OF THERAPY IN TRIGEMINAL NEURALGIA: RESULTS OF TREATMENT WITH TYPHOID VACCINE IN EIGHTEEN CASES. E. R. SCHMIDT and J. M. SULLIVAN, Wisconsin M. J. **38**:635 (Aug.) 1939.

In evaluating the results of treatment of trigeminal neuralgia with hyperpyrexia, Schmidt and Sullivan chose typhoid vaccine because of its ease of administration and handling, treating 18 patients. Injections at about biweekly intervals, starting with a dose of 10,000,000 killed organisms, were given intravenously, and the doses were stepped up by 10,000,000 or 20,000,000 each time until a good thermal reaction was obtained. Early in their series they learned that results could be obtained as readily with a mild fever response as with a high thermal reaction. The majority of their patients were hospitalized for their treatments, but several ambulatory patients were treated and no ill effects were encountered. Five patients obtained more than 80 per cent relief, and they were satisfied to control their residual tic with mild analgesics or Christian fortitude rather than

to submit to further therapy. In 5 other patients, relief was complete and continuous. Four patients experienced complete relief for from two to four months and failed to respond to a second course of vaccine therapy, so that injections of alcohol were necessary for the further control of the tic. Three patients obtained 50 per cent relief or less and needed injections of alcohol to complete their treatment. Only 1 patient in the series failed to show some amelioration of symptoms after vaccine therapy; the sensory root of the trigeminal nerve was resected, and complete relief ensued. Women showed a slightly better response than men to this form of treatment. Snake venom in a trial group proved unsuccessful in relieving pain of this type.

J. A. M. A.

HEREDO-FAMILIAL TENDINOUS AREFLEXIA WITHOUT PUPILLARY CHANGES. L. VAN BOGAERT, J. Neurol. & Psychiat. **2**:193 (July) 1939.

Van Bogaert reports the occurrence of a heredofamilial condition characterized by generalized or partial tendinous areflexia in two families. In the first family, of 7 children, the syndrome occurred in a brother and 2 sisters. In the second family, of 11 children, it was present in 3 sisters and in the son of one of them, the tendinous areflexia affecting all or only some of the tendon jerks, including the jaw jerk. The tendon reflexes could not be obtained by any of the methods of reenforcement or by injection of epinephrine. The cutaneous reflexes were always present. The condition was unaccompanied by pupillary changes or other neurologic or mental signs. The condition was independent of somatic abnormalities or trophic changes and was not the result of hereditary syphilis. Autopsy in 1 case showed no abnormality in the central or the peripheral nervous system, except for the left sciatic nerve, which contained a typical venous angioma and only a few myelinated fibers. The author suggests that the areflexia in all cases may depend on such angiomatous malformations in the nerve trunks, although further studies are necessary to substantiate this. These angiomas represent anomalies in the development of the primitive vascular plexuses of the nerve sheaths. Van Bogaert regards the condition as a constitutional disorder of rare occurrence, which is to be differentiated from other types of areflexia of syphilitic origin which are associated with other neurologic disorders.

MALAMUD, Ann Arbor, Mich.

LUMBOCRURAL NEURALGIAS OF COLONIC ORIGIN. M. BRULÉ and H. GARBAN, Presse méd. **47**:1061 (July 5) 1939.

Brulé and Garban direct attention to the frequency with which patients who have disorders of the large intestine complain of pain in the kidneys. The pain is localized in the lumbar region, from the twelfth rib to the iliac crest; it is localized especially in the superior third of the buttock, a little outside the sacroiliac symphysis, and in the root of the thighs, from the anterosuperior iliac spine to the pubic symphysis. At the fold of the groin it radiates in toward the spermatic cord or the round ligament, to the scrotum or the labia majora, and toward the internal surface of the thigh. From the anterior extremity of the iliac crest it crosses the anteroexternal surface of the thigh, encircles the knee and at times descends along the leg to the great toe. Walking is painful because of the lumbar rigidity and the heaviness in the lower limbs. The pains are intensified by brusque movements and lessened by rest and warmth. They are influenced directly by changes in the intestinal condition; they are aggravated by increased constipation or a mistake in diet and subside only with amelioration of the colonic disorder. The most constant of these painful points are the gluteal, femorocutaneous, crural and obturator. These neuralgic points correspond to the emergence of sensory branches of the lumbar nerve plexus. There is no neuralgia in the region of the sciatic nerve. Lasègue's sign is not elicited, whereas the inverse maneuver, that is, hyperextension of the thigh onto the pelvis, often provokes a severe pain at the femorocutaneous and the crural points. The lumbosacral neuralgias develop

in organic disorders of the colon, which may be of the acute or the chronic type. In cases of acute disorders, such as appendicitis and diverticulitis, the pain spreads rapidly over the lumbar region, the buttocks and the inferior members, and it regresses again with the same rapidity. In chronic lesions, such as cancer, only a single nerve branch, the femorocutaneous or the crural, is usually involved. Slow progressive evolution provokes veritable neuritis and terminates in paresthesia with partial atrophy of the muscles of the thigh and abolition of the patellar reflex. Like the colonic pain, lumbocrural neuralgia varies in localization; it may be unilateral or bilateral or oscillate from one side to the other. One day it may be localized in the lumbar region and the following day in the buttocks or the thigh. Often it appears in an atypical form; there are vague pains which the patients designate as rheumatic. The author says that treatment of the cause, that is, of the intestinal disorder, is more effective than local therapy.

J. A. M. A.

Relation of Migraine and Neuralgias of the Face. J. Haguenau and H. Kaufmann, Rev. d'oto-neuro-opht. **17**:321 (May) 1939.

Certain neuralgias, so-called migraine neuralgias, are distinct from tic douloureux and constitute the equivalent of migraine. In "migraine neuralgia" the area of the pain and cutaneous hyperesthesia is not strictly limited to the distribution of one branch of the fifth nerve but encroaches on the field of several branches, and sensorial excitations and meterologic changes affect the sufferers more easily than they do persons with essential neuralgia. Migraine neuralgias are distinguished from other sympathalgias by not being continuous, by affecting especially females and sufferers from long-standing migraine and by their evolution. Like migraine, they tend to react to episodes of the sexual life, appearing at the menstrual period or at the beginning of the menstrual cycle, disappearing during pregnancy or amenorrhea and being modified by the menopause. Like migraine also, the attacks are sometimes almost continuous, or they may disappear over a long period or alternate with crises of migraine. They are not cured by injection of alcohol into the nerve. This is the only type of neuralgia of the face that is akin to migraine.

Dennis, San Diego, Calif.

Pathologic Changes in Polyradiculitis. L. Benedek and A. Juba, Deutsche Ztschr. f. Nervenh. **149**:205, 1939.

Benedek and Juba report a case, with necropsy observations, in which the clinical diagnosis was chronic bulbar paralysis. Neurologic examination revealed bilateral involvement of the cranial nerves and atrophy, with fibrillary twitchings in the muscles of the shoulder girdle. The reflexes of the upper extremities were diminished; those of the lower extremities were increased. At autopsy myelin degeneration of the nerves of the extremities was observed. The damage was most marked in the sciatic nerves. Several lymphocytes were seen perivascularly and within the parenchyma of the nerves. There was marked infiltration of the anterior roots. The cervical part of the spinal cord showed extensive damage; there were glial nodules, perivascular lymphocytic infiltration and degenerated motor ganglion cells in this part of the spinal cord, as well as in the medulla oblongata and pons. There was marked proliferation of the microglia perivascularly and in the glial nodules in the substantia gelatinosa of the trigeminal nerve and within the tract of Burdach. Another patient, aged 65 years, died after six weeks. He had extensive muscle pareses and diffuse sensory impairment. The total protein content of the spinal fluid was 160 mg. per hundred cubic centimeters, but the cell count was normal. There was marked tenderness on pressure of the nerve trunks. Only the sciatic nerves, lumbar ganglia and thoracolumbar portion of the spinal cord were examined histologically. The nerves showed destruction of myelin and axis-cylinders and perivascular infiltrations. The authors believe that the disease was caused by a virus.

Adler, Boston.

Vegetative and Endocrine Systems

THE RATE OF INCREASE IN HYPOPHYSEAL GONADOTROPIC CONTENT FOLLOWING OVARIECTOMY IN THE RAT, WITH OBSERVATIONS ON GLAND WEIGHTS. H. D. LAUSON, J. B. GOLDEN and E. L. SEVRINGHAUS, Endocrinology **25**:47 (July) 1939.

The authors studied the increase in gonadotropic potency of the hypophysis following ovariectomy in female rats aged 24 weeks. The gonadotropic factor in females ovariectomized five, ten, twenty, thirty, sixty and one hundred and twenty days prior to autopsy was evaluated in terms of an arbitrary "uterine unit" and compared with that of normal female rats of the same age. It was found that the potency for each pituitary gland increased in relation to the time after gonadectomy, as follows: 3.7, 7, 20.7, 31.2, 52.7 and 51.9 times the normal. The "uterine unit" is described by the authors as equal to the uterine weight produced by 1 mg. of whole fresh pituitary gland from female rats ovariectomized twenty days prior to autopsy. Assay was accomplished by the injection of 0.5 cc. of a suspension of the macerated pituitary gland in distilled water twice daily for three days into 22 day old female rats weighing from 35 to 40 Gm. Autopsy was performed on the fourth day and the uteri and ovaries weighed. It was found that body weight increased from an average of 216 Gm. for the normal rats to an average of 274 Gm. for those ovariectomized one hundred and twenty days before autopsy; body length increased from an average of 20.6 cm. for the former to one of 21.7 cm. for the latter. There was no consistent effect on the weights of the pituitary gland and thyroid, and no significant atrophy of the adrenals was observed. Hypertrophy of the thymus reached a maximum increase of 240 per cent over the normal by the thirtieth day after ovariectomy. Increase in weight of the kidneys was roughly proportional to body growth, except in those castrated sixty and one hundred and twenty days before autopsy.

PALMER, Philadelphia.

THE INFLUENCE OF THE ANTERIOR PITUITARY GLAND ON PROTEIN METABOLISM. I. A. MIRSKY, Endocrinology **25**:52 (July) 1939.

Mirsky studied the effects in dogs of subcutaneous administration of a crude extract of the anterior lobe of beef pituitary gland in massive doses equivalent to 2 Gm. of fresh anterior lobe per kilogram of body weight. The results indicate that there follows a decrease in the protein breakdown in normal dogs, as shown by the retention of nitrogen in the tissues, an increase of approximately 61 per cent in the rate of protein catabolism in depancreatized dogs and an increase of approximately 80 per cent in eviscerated dogs. It is suggested by the author that the anterior lobe of the pituitary gland exerts a direct effect on the muscles, which in the eviscerated and depancreatized dog is in a direction opposite that observed in the intact animal. It is postulated that the synthesis of muscle protein consequent to the administration of extracts of anterior lobe may be dependent on the simultaneous stimulation of the pancreas. That the pancreas has such a function in preventing the breakdown of protein and may actually synthesize protein is indicated by the observation that insulin exerts a definite nitrogen-sparing action in the normal, the eviscerated and the depancreatized dog.

PALMER, Philadelphia.

ENDOCRINE DYSCRASIAS ASSOCIATED WITH CONDUCT DISORDERS IN COLORADO SPRINGS CHILDREN. C. S. GYDESEN and B. J. MURPHEY, Rocky Mountain M. J. **36**:462 (July) 1939.

In view of the contradictory and confusing reports regarding the relationship, or lack of relationship, between behavior disorders in children and the various types of endocrine dyscrasias, Gydesen and Murphey reviewed 64 cases of children who had been examined by a psychiatrist in a child guidance clinic and also by an endocrinologist in private practice. Thirty-six of these children were referred to the endocrinologist by the child guidance clinic as presenting a possible endo-

crine dyscrasia. The 36 cases were selected from a series of 313 consecutive cases in which the children were fully studied at the child guidance clinic. Disorders of the thyroid (32 cases) and pituitary gland (18 cases) were by far the most common conditions discovered. All the children treated specifically showed definite improvement in their school and social adjustment with endocrine therapy.

J. A. M. A.

THE JUVENILE FORM OF THE ADRENO-GENITAL SYNDROME. J. S. RICHARDSON and W. R. S. DOLL, Brit. M. J. **1**:501 (March 11) 1939.

Richardson and Doll report the case of a girl aged 7 with the mentality and physical development of a child aged 12. Pubic hair had been noted since the age of 18 months, and the voice had been gruff since the age of 3 years. Pseudohermaphroditism was present. Death followed adrenalectomy. Postmortem examination disclosed marked hyperplasia of the cortex of the adrenal gland, with ponceau-fuchsin staining reaction throughout the cortex. The case is classified as a typical instance of the juvenile type of the adrenogenital syndrome.

ECHOLS, New Orleans.

CUSHING'S SYNDROME: REPORT OF A CASE IN WHICH NO ENDOCRINE TUMOUR WAS FOUND. G. HALL, C. E. KELLETT and G. E. STEPHENSON, Lancet **1**: 862 (April 15) 1939.

The authors point out that 22.5 per cent of 1,000 hypophyses presented adenomas and that of these only 27.2 per cent were basophilic (Costello). This, in their opinion, tends to render the term pituitary basophilism of no significance. Since this clinical syndrome has been reported with both basophilic and chromophobic tumors of the pituitary gland and with tumors of the adrenal cortex and thymus, its presence without evidence of any endocrine tumor is interesting. The authors report the case of a man aged 26 who had been gaining weight for five years. During the last two years he had complained of severe pains in the frontal region of the head, had noted striations over the abdomen and arm pits and had had a number of furuncles. Shortly, there developed difficulty with his eyesight; he complained of nosebleed and shortness of breath and consumed large amounts of water. He was obese and short, and the extremities showed a normal amount of adipose tissue. There were a mild degree of exophthalmos, marked perspiration and bright purplish abdominal striations. He had some difficulty in concentrating. There were a visual defect in the left temporal field and questionable swelling of the optic disk on the same side. No other abnormal conditions were observed. The dextrose tolerance was decreased. The erythrocyte count was 6,000,000 and the leukocyte count 25,000. The urea clearance dropped from 98 to 57 per cent of normal. The urinary output was from 80 to 100 ounces (2.3 to 2.9 liters). The Ashheim-Zondek reaction was negative. The patient died after an operation for removal of warts present under the prepuce and in the natal cleft. Necropsy revealed only enlargement of the heart, evidence of bronchiectasis and small collections of basophilic cells in the pars distalis (anterior lobe) of the pituitary gland, though these were not considered of adenomatous proportions. Dr. A. C. Crooke, who examined a specimen of the pituitary gland, observed the hyaline cells which he had previously described in cases of pituitary basophilism.

KRINSKY, Boston.

Muscular System

STUDIES IN DYSTROPHIA MYOTONICA: HEREDITARY ASPECTS. ABE RAVIN and JAMES J. WARING, Am. J. M. Sc. **195**:593 (May) 1939.

Ravin and Waring report on the hereditary aspects of dystrophia myotonica. Four family trees were studied; 12 cases of the disease were found among 33 members examined. At least 4 additional cases of the disease occurring in the

family could not be investigated. The disease appears to be due to a dominant mutation, which is at first manifested by very slight and few signs, notably cataract. The gene may be transmitted through several generations with no apparent manifestations, as shown by pedigrees in which apparently scattered cases of dystrophica myotonica may be traced back six or seven generations to a common ancestor. Finally, in one generation the disease becomes severe enough and sets in early enough to be clearly recognized. In such cases, persons with the disease transmit it to their children as a simple dominant character. The phenomenon of increase in the severity of disease in succeeding generations has been called "potentiation." The evidence points to the conclusion that the condition is due to a single gene or to several genes closely linked, for the following reasons: (1) The vast majority of those affected sooner or later show all the manifestations of the disease; (2) the complete syndrome may occur in children of parents who show only one of the signs, and (3) if crossing over and consequent dissociation of the symptoms of the disease were frequent in early generations, the complete syndrome would not occur so frequently and individual symptoms so infrequently in later generations.

MICHAELS, Boston.

POTASSIUM CONTENT OF MUSCLE IN DISEASE. J. N. CUMINGS, Brain **62**:153 (June) 1939.

Cumings records the potassium content of muscles in a variety of muscle diseases, with special reference to dystrophia myotonica and myasthenia gravis, in which conditions he thinks no similar investigations have been made. The effect of the administration of prostigmine on the muscle potassium has been studied. The potassium content of affected muscles was normal in cases of progressive muscular atrophy, simple atrophy, Charcot-Marie-Tooth disease, myositis, wasting associated with cerebral tumor and peripheral neuritis. Muscles containing a low potassium concentration were seen in cases of pseudohypertrophic muscular dystrophy, peroneal atrophy, marked atrophy with fibrous tissue replacement and myopathy with marked fibrosis and myotonia. The muscles in this group of diseases contain a large excess of fat or of fibrous tissue. Muscles from 2 normal subjects, 2 patients with myotonia and 2 with myasthenia gravis were investigated. Muscles from the normal patients showed no appreciable alteration in potassium content after the administration of prostigmine, but the potassium content of muscles in the cases of myotonia and of myasthenia after administration of prostigmine approached the normal level. Concurrent with the return to a normal potassium level there was a return to normal muscle function in patients with myasthenia gravis. Patients with myotonia showed no clinical improvement as regards either the myotonia or the muscular function, although the potassium content approached the normal; this was not surprising, as all the muscles showed signs of atrophy.

J. A. M. A.

CONGENITAL MYOTONIA IN THE GOAT. G. L. BROWN and A. M. HARVEY, J. Physiol. **96**:11P, 1939.

Brown and Harvey studied a strain of goats with congenital myotonia. They observed the effects of electrical stimulation of the nerve fibers and of acetylcholine on the voluntary muscles. They conclude that the abnormality is in the muscle fibers and not in the neuromuscular transmitting apparatus.

THOMAS, Philadelphia.

Society Transactions

PHILADELPHIA NEUROLOGICAL SOCIETY

J. C. YASKIN, M.D., *President, in the Chair*

Regular Meeting, April 28, 1939

ADIE'S SYNDROME: REPORT OF A CASE. DRS. JOSEPH WALDMAN (by invitation), JOHN T. EADS (by invitation) and ROBERT A. MATTHEWS.

A case of Adie's syndrome in a white woman aged 27, with neurotic tendencies, is reported. In addition to tonic enlargement of the left pupil, she had marked diminution of reflexes in the upper extremities. The effect of various mydriatic and miotic drugs on this patient was discussed, together with a review of the literature.

DISCUSSION

DR. ROBERT A. MATTHEWS: I shall comment only on the personality characteristics which have been noted in this case and in other cases in the literature. A large majority of persons with this syndrome are young women who show emotional instability; this suggests the relationship between emotional factors and physical or physiologic disturbances.

I have seen only 1 other patient with this syndrome—a girl aged 18 who was suspected of having organic disease of the central nervous system but was found to be profoundly neurotic. Our patient has been emotionally maladjusted for years. The important thing is to recognize the benign nature of the clinical signs.

DR. EDWARD A. SHUMWAY: It seems to me that most of the cases that have been reported were those of Irish girls. Curiously, that was brought out in the discussion of a case recently reported before the section on ophthalmology of the College of Physicians of Philadelphia. From a practical standpoint that can mean little. It seems to me that the less the patient's attention is called to a peculiarity of this sort the better it is for the patient.

DR. TEMPLE FAY: Why should the condition be present only on the left side? What known pathologic lesion is associated with it?

DR. JOSEPH WALDMAN: As to the side on which the condition is present: The only hypothesis I can offer is that the left side is supposedly the dominant side of the brain in right-handed people.

DR. TEMPLE FAY: Are these cases, those in which the condition is present on the left side, all of right-handed persons?

DR. JOSEPH WALDMAN: Yes. Those that have been reported are. No definite pathologic lesion to account for the condition has been described.

TUMOR OF THE THIRD VENTRICLE CAUSING HYDROCEPHALUS: REPORT OF A CASE. DRS. EDWARD A. SHUMWAY (by invitation) and FRANCIS C. GRANT.

A case of tumor of the third ventricle which caused chronic internal hydrocephalus is reported. The patient, then a boy aged 10, was first seen in 1920, when he complained of headaches and vomiting. Examination of the eyes showed low grade papilledema, reduction of vision, contraction of visual fields and paresis of a levator muscle of the eyes. He was referred to Dr. Charles H. Frazier, who found disturbed cerebellar function, increased intracranial pressure, ataxia of the upper extremities and dysmetria. A suboccipital decompression was done by Dr. Frazier, and the dural tension was found to be above normal, but no growth was seen. Puncture of the cisterna basalis was carried out, but there was no escape of fluid. The boy made a good recovery; the optic neuritis

disappeared; the fields returned to normal, and vision improved. For three years he attended school, doing well in his school work; then attacks of unconsciousness appeared, during some of which he hurt himself in falling. The circumference of the head increased from 61 to 65 cm.

In June 1925 he was readmitted to the hospital. His mental condition had changed, but there was no sexual precocity. With local anesthesia, dye was introduced into the third ventricle; it did not appear in the spinal fluid in twenty minutes, showing that the ventricle was obstructed, nor did it appear in the urine in five hours. A roentgenogram of the skull showed marked atrophy of the cerebral convolutions. Vision was 6/9 in the right eye and 6/12 in the left; the optic nerves showed moderate atrophy.

Later in 1925 there developed generalized convulsions, which were not definitely epileptiform, and the boy failed mentally. He was admitted to an institution for epileptic patients and died in 1937, when 25 years of age, of cerebral hemorrhage resulting from an accidental blow on the head. Autopsy, performed at the Hospital of the University of Pennsylvania by Dr. Bernard J. Alpers, showed a very large brain, which weighed 2,220 Gm., the size being due partly to internal hydrocephalus and partly to an actual increase in brain substance. Over the left cerebral hemisphere was a large subdural hematoma. Sections of the brain revealed large gyri in which the white matter showed small hemorrhagic areas. These occurred also in the cortex. Filling the third ventricle was a tumor which was adherent to the floor of the ventricle and extended through the aqueduct into the fourth ventricle, invading the right lateral wall of the pons. It had no relation to the pineal body and seemed to arise from the ependyma, to which it was firmly adherent. There was a high degree of internal hydrocephalus involving the lateral ventricles, but the fourth ventricle was not dilated. The corpus callosum was thin, and the basal ganglia were much compressed by the dilated ventricles.

DISCUSSION

DR. FRANCIS C. GRANT: This case is interesting for a number of reasons. Suboccipital decompression was instrumental in prolonging this boy's life in reasonable comfort for seventeen years, although the tumor was not revealed. Dr. Walter Dandy (Benign Tumors in the Third Ventricle: Diagnosis and Treatment, Springfield, Ill., Charles C. Thomas, Publisher, 1933) reported that of a group of 10 patients, 3 were alive six years after operation. That, of course, was after direct surgical attack; it is interesting that in the present case, in which no attempt was made to remove the tumor, the boy was able to live in relative comfort for seventeen years. How that happened is one of the interesting problems. As shown in a lantern slide, the blocking of the aqueduct was not complete, and presumably therefore there was always a certain amount of circulation of cerebrospinal fluid. At one time circulation must have been interfered with, because rhinorrhea developed and continued for from eighteen months to two years. It was always a miracle to me how this boy could be going about. He would get up in the morning and lose 25 or 30 cc. of fluid from his nose. If he coughed or strained or made any kind of sudden movement he would have a spurt of cerebrospinal fluid from his nose; yet meningitis never developed. Why did he have epilepsy? He certainly did not have a lesion associated with any of the usual areas of the brain with which one connects epileptic attacks. I am not sure he had what would be called epilepsy. I never saw him in an attack. I could not be certain from his mother's description that the seizures were epileptiform. They may have been due to the internal hydrocephalus. The manner of death was again curious, for he had only a slight injury. He was pushed over by a fellow epileptic patient during a tussle and hit his head. He was an obstreperous lad by that time, and I think every one was glad he had a fall. He was taken to the infirmary and died. His brain showed a chronic subdural hematoma. It would have been interesting to have seen what his expectation of life would have been had he not been injured. Certainly, the results of decompression were much better than could have been accomplished by any surgical procedure, because this was an infiltrating neoplasm.

I suppose that now with present knowledge of ventriculography, it would have been a simple matter to diagnose and localize the lesion. In 1921, before the value of ventriculography was recognized, nothing was attempted. The simple decompression in some way must have permitted readjustment of the spinal fluid circulation, which was maintained during the next seventeen years. I should have been pleased if I had removed the tumor and the boy had been alive seventeen years afterward.

DR. B. J. ALPERS: From the standpoint of pathology, it is well to point out that many neoplasms which are spoken of as tumors of the third ventricle are not really such. They are tumors which involve the adjacent brain substance, and belly out into the third ventricle. Only from that standpoint should they be spoken of as tumors of the third ventricle. A great deal of the confusion with regard to tumors of the third ventricle has come from regarding infiltrating tumors which project into the third ventricle as really tumors of the third ventricle. Actually, primary tumors of the third ventricle are rare. There are some colloid tumors which fill the third ventricle; they are unusual. Rarely does one see dermoid cysts, or other cysts, arising primarily in the third ventricle. If one considers the primary tumors of the third ventricle the matter becomes simplified from the pathologic standpoint, but confused from the clinical. In these cases there is a history of increased pressure and possibly of intermittent headache, and, as Oldberg and Eisenhart have pointed out, in a small percentage of cases there is a history of personality and emotional deviations. I do not think it is possible to make more than a guess at a diagnosis of tumor of the third ventricle in most instances. In cases in which there is increased intracranial pressure without localizing signs, one is entitled to a guess of tumor blocking the ventricle.

DR. JAMES S. DEAN: Was the tumor an astrocytoma?

DR. B. J. ALPERS: It was a fibrous tumor, and a very slowly growing one.

DR. JAMES S. DEAN: The question is: Might the universality of the symptoms and the convulsive seizures be accounted for on the basis of acute internal hydrocephalus, which suddenly compromised the circulation and function of the entire cerebrum? When the pressure became sufficiently high may there not have been spontaneous decompression, since there was only a partial obstruction?

DR. B. J. ALPERS: I do not know that I can answer that question. Maybe Dr. Grant can. It is possible that some of the intermittent symptoms could be explained in that way, but not the convulsions. I think that the convulsions may in part be explained by the fact that there was a lesion in the cortex.

DR. JAMES M. DEAN: Has Dr. Alpers any explanation for the increase in the amount of cerebral tissue?

DR. B. J. ALPERS: No. The brain, incidentally, was the largest that I ever saw. It was really a large brain, in addition to being hydrocephalic.

DR. TEMPLE FAY: Is it possible that the enlargement of the brain may have been one of the factors in the early increase of pressure, or was the tumor of seventeen years' existence?

DR. B. J. ALPERS: I do not know. I only know it was a very slowly growing tumor. It is conceivable that this tumor may have existed for seventeen years.

DR. EDWARD A. SHUMWAY: I am glad Drs. Frazier and Grant did not perform a more formidable operation. They could not have removed the tumor, because it was infiltrative. In Weisenburg's cases there was a free tumor which acted as a ball valve and shut off the flow of the cerebrospinal fluid from the third ventricle and caused attacks of unconsciousness. I am not sure that in our case the attacks were truly epileptiform. At the Vineland institution they considered them of that type, but the patient was not examined by a man who was entirely competent to make such a diagnosis. In many respects the attacks were not epileptiform: The patient did not have an aura and did not froth at the mouth, cry out or hurt himself. Although the convulsions were general, they were not followed by drowsiness. To me, the case was most interesting,

from the fact that the boy was able, after operation, to go on with his school work. He had a marvelous head for figures, and never forgot a telephone number. In mathematics he was very good, but later, with the increasing degenerative changes, his memory failed and he was unable to keep up any consecutive work.

RADICULAR PAIN ASSOCIATED WITH INTRATHORACIC TUMORS. DR. PAUL SLOANE.

CASE 1.—J. D., a white man aged 59, a plumber, gave a history of carcinoma of the bladder treated by roentgen therapy. He complained of pain between the scapulas, in the right shoulder and radiating down the right arm. There had been loss of 12 pounds (5.4 Kg.) in weight in six months. There were: a Horner's syndrome on the right side, weakness in movements of the right upper limb; fulness of the right supraclavicular space; evidence of an apical mass on direct physical and roentgen examination; erosion of the second and third ribs on the right side and the bodies of the second and third thoracic vertebrae. Relief was obtained by chordotomy. Death occurred ten months after the onset of symptoms.

Autopsy.—The diagnosis was: scirrhous carcinoma of the stomach, with metastases to the adrenal glands and apex of the right lung; destruction of the first three ribs on the right side, near their vertebral ends.

CASE 2.—H. C. W., a white man aged 51, an auditor, complained of pain in the left side of the chest, radiating into the left upper extremity, and loss of 40 pounds (18.1 Kg.) in weight in nine months. There were: a Horner's syndrome on the left side; generalized atrophy and weakness of the muscles of the left arm; a spontaneous sweating level between the second and the fifth dorsal dermatome on the right; roentgenographic evidence of tumor at the apex of the left lung, with destruction of the first and third dorsal vertebral segments. Death occurred eleven months after the onset of symptoms.

Autopsy.—The diagnosis was: bronchiogenic carcinoma of the apex of the left lung, with metastases to the brain and both adrenal glands; erosion of the first rib and seventh cervical and first and second thoracic vertebrae.

CASE 3.—J. W., a white man aged 55, a grocer, complained of sharp pain in the left side of the chest, which was increased by respiratory movements and relieved by fixation of the chest; marked emaciation; a sharply demarcated area of profuse sweating between the fifth and the ninth dorsal dermatome on the left, and hyperesthesia of the chest wall. A diagnosis of bronchiectasis was made. Chordotomy gave partial relief from pain. Death occurred fourteen months after the onset of symptoms.

Autopsy.—The diagnosis was: bronchiogenic carcinoma (bilateral), with extension to the pleura and adjacent vertebra; bronchiectasis.

CASE 4.—T. H., a white man aged 53, an insurance agent, complained of burning pain over the left side of the chest anteriorly and the left scapula; he had lost 30 pounds (13.6 Kg.) in weight. There were: unilateral sweating on the left side from the face down to the sixth thoracic segment, associated with coolness of the skin and vasomotor lines; roentgen evidence of a neoplastic process at the apex of the left lung, with erosion of the pedicles and bodies of the third and fourth thoracic vertebrae, which later extended to include the third, fourth and fifth ribs. The diagnosis of carcinoma was confirmed by a biopsy specimen taken with a needle; complete relief from pain followed chordotomy and posterior rhizotomy.

Comment.—In summarizing the material in the 4 cases presented, as well as the reports in the literature, it may be said that the differential diagnosis of pain due to intrathoracic tumors depends on the following criteria: All patients are elderly persons suffering from a severe debilitating disease, which causes rapid loss of weight and strength. Pain is frequently an early symptom; it is unilateral and increases progressively in severity, is characterized by a sharp shooting quality and radiates along the distribution of one or more spinal roots.

It is increased by movements of the spine and factors which raise intracranial pressure, such as coughing or sneezing. Muscular weakness, hyperesthesia and sympathetic disturbances in the same segmental distribution as the pain are frequently associated. The diagnosis of tumor may be confirmed by physical examination and roentgen demonstration of a pulmonary shadow with erosion of the ribs and the vertebrae, although these signs may be absent. This was true in the third case, in which roentgen and physical examination did not reveal the actual cause of the symptoms. Here the correct diagnosis might have been suspected from the diagnostic character of the pain and its associated symptoms. Occasionally, bronchoscopy and biopsy of a mass in the neck or axilla may be of assistance. The persistence of pain and its progressive increase in severity must be emphasized, since there are few conditions that give rise to these symptoms.

The type of lesion varies. The tumors usually arise from the lung, but they may also be extrapulmonary. The most common tumor is carcinoma, either primary or metastatic, although sarcoma and other tumors have been described. Although Pancoast suggested that his cases represented a specific type of lesion, namely a tumor arising in the embryonic epithelial rests of the branchial apparatus, he did not have sufficient evidence to support his theory. Lately, however, Fried was able to confirm the fact that the branchiogenic carcinoma may occur in the region of the pulmonary apex. He has suggested the names of "sternoclavicular branchioma" for this type of tumor.

Nonmalignant tumors produce localized symptoms, depending on their location. They do not tend to implicate the adjacent structures, in striking contrast to malignant growths, which do not confine themselves to one tissue, but spread out and steadily encroach on whatever structures they meet in their path. This is particularly true of carcinoma, which may invade or perforate tubes and vessels, compress nerves and erode bone. The nerves in the thorax which may be involved are the spinal roots, brachial plexus, sympathetic trunk and phrenic, recurrent laryngeal and vagus nerves. Intrapulmonary tumors are painless unless they come to the surface and irritate the pleura or extend into the mediastinum. If the growth occupies the anterior mediastinum and presses on the sternum the pain will be poststernal. If it projects into the posterior mediastinum, i. e., where the spinal roots are situated, the pain will be sharp and lancinating. It is with the latter class of tumors that I am particularly concerned in this paper.

The tumor in growing impinges on the spinal roots as they emerge from the intervertebral foramens, just before the sympathetic rami are given off. It thus happens that pain may arise before the bony structures are invaded by the growth. The pain radiates in a characteristic manner, depending on the particular root or roots involved. If the lesion is in the lower cervical and upper thoracic segments the pain spreads down the arm; if in the lower thoracic segments it radiates around the thoracic wall along the distribution of the intercostal nerves. If the lesion is essentially an irritative one hyperesthesia will be present in the affected area, and there will be increased sweating and fall in surface temperature over the affected area. In cases in which the sympathetic fibers are destroyed, however, Horner's syndrome and complete absence of sweating may be present. The symptoms, of course, are primarily unilateral. Involvement of the brachial plexus may occur but, practically speaking, it is difficult to know whether the brachial plexus or the corresponding spinal roots are involved. To all intents and purposes it makes little difference, since symptoms point to a lesion in the same general locality. It will be seen that no essential difference in the mechanism of pain production exists between tumors situated in the apex of the lung, the so-called tumors of the superior pulmonary sulcus, and those situated elsewhere in the thorax. Furthermore, it can be shown pathologically that any type of tumor may occur at the apex of the lung, and not necessarily a specific type, as suggested by Pancoast.

Treatment of intrathoracic tumors is discouraging. Direct surgical attack on the tumor does not commend itself because of the frequent presence of metastases and the dangers inherent in surgical intervention on the lung. Roentgen

therapy has been unsuccessful because most of such tumors are radio-resistant. In the large majority of cases the only treatment that can be adopted is palliative, intended to relieve the pain. It would, therefore, be advisable to consider chordotomy or posterior rhizotomy as soon as the condition is recognized, so as to spare the patient all unnecessary suffering.

DR. TEMPLE FAY: Patients with this condition are probably the most pathetic I have ever encountered. Suffering is truly intense, and certainly chordotomy is a means to an end, as Dr. Chamberlain has said. If the condition is recognized early enough and chordotomy given a chance, at least some of the unnecessary suffering may be spared, because even morphine does not control the pain these patients have. The condition is rapidly fatal. In cases in which I have operated lately there has not been expectancy of many more weeks or months of life, but all patients have expressed the feeling that it should have been done earlier.

CEREBROSPINAL PROTEIN: STATISTICAL STUDY OF ITS CLINICAL AND PATHOLOGIC SIGNIFICANCE. DR. JAMES S. DEAN.

A statistical study of the quantitative ranges of the total protein content of the cerebrospinal fluid in 279 unselected cases of all types from laboratories of the Philadelphia General Hospital was undertaken, and the clinical diagnosis and the protein figure were correlated in each instance. The cases were then regrouped according to the general pathologic nature (and the quantitative protein ranges for each pathologic group charted) as follows: (1) no neurologic or psychiatric disorder; (2) "functional" nervous and mental disorders; (3) congenital disorders; (4) degenerative conditions; (5) intoxications; (6) circulatory disorders; (7) traumatic conditions; (8) infections; (9) infectious granulomas; (10) neoplasms; (11) undiagnosed disorders of the central nervous system. The technic employed in the quantitative protein determinations was the Andersch-Gibson method. The percentage of cases in each pathologic group in which protein values were above or below 40 mg. and above or below 60 mg. per hundred cubic centimeters was determined.

In 68 per cent of the total 279 cases protein values below 60 mg. were shown. Of cases in which the protein figures were above 60 mg., 49.3 per cent were those of infectious granuloma (syphilis and tuberculosis); 13.8 per cent were those of neoplasms and vascular disorders, respectively; 11.1 per cent were those of so-called functional disorders (?), and 7.4 per cent were those of nonpyogenic infections of the central nervous system. (Cases of pyogenic meningitides were not included in this series, protein determinations not having been conducted, presumably because the other studies of the spinal fluid rendered the diagnosis obvious.) In 84 per cent of cases of infectious granuloma and in 77 per cent of cases of neoplasms protein figures were above 40 mg. per hundred cubic centimeters.

From a statistical standpoint, this study strongly suggests that the pathologic states most apt to elevate the spinal fluid protein are conditions tending to alter the blood-brain barrier, i. e., infection, vascular disease and neoplasm (the last producing passive congestion by mechanical blockage of neighboring veins, particularly the venous effluent veins of the choroid plexuses in cases of tumor of the brain). Moreover, in instances in which elevation of the total protein constituted the only abnormality in the spinal fluid, this alone was believed to indicate strongly the presence of organic disease of the central nervous system, the chances being that the condition was either neoplasm or vascular disease.

Theories of origin of the cerebrospinal fluid protein in physiologic and pathologic states were presented. I regard the greater part of the protein in physiologic states as being transferred from the blood plasma through the choroid plexuses. In pathologic conditions, elevations of protein can be ascribed to altered permeability of the "hematoencephalic barrier," vascular permeability here being influenced by the same factors as elsewhere in the body, i. e., (1) the condition of the vessel wall and (2) the temperature and pressure (both mechanical and osmotic) relationships inside and outside the vessel wall. Attention is called

to the relatively scant interest which has been shown in decreased protein content of the cerebrospinal fluid, such as occurs in the spinal and ventricular fluid in many cases of obstructive internal hydrocephalus and in cases of hydremia (such as results from forced drainage). Objections may be raised to the concepts that "irritative ependymal changes" and "products of hemorrhage and necrosis" are responsible for elevations of protein in cases of tumors of the brain.

The quantitative determination of the spinal fluid protein is thought to offer a convenient index to the permeability of the hematoencephalic barrier. Moreover, further study of the proteins should clarify certain problems, such as the colloidal gold curves and the passive transfer of immune bodies from the blood stream to the spinal fluid (as might be the case when the spinal fluid is Wassermann positive and there are no neuropsychiatric clinical signs).

DISCUSSION

DR. ROBERT A. GROFF: Dr. Dean is to be congratulated on the clearness with which he presented his subject. The explanation for the increase in protein content of the spinal fluid in certain patients with tumors of the brain as a mechanical result of compression of the veins of Galen is interesting. I talked with Dr. Dean about this some time ago. If this theory is true, it seemed to me that pineal tumors would be ideal proof. I investigated the records in a case of pineal tumor and found that the protein content of the spinal fluid was increased. However, the method used to determine this was qualitative rather than quantitative. Although in this case there were no figures for the protein content of the spinal fluid, I believe that the findings support Dr. Dean's theory.

I wish to comment on one phase of Dr. Dean's work; that is the method of protein determination. I believe that at present the Kjeldahl method is employed for determining the protein content of the spinal fluid. Most chemists admit that errors occur frequently with this technic. For this reason, I have been consulting with the chemist at the Graduate Hospital of the University of Pennsylvania to see if a more reliable method can be used. He is working on this problem, and it appears that the method used for determination of protein in the blood can be applied to the spinal fluid. It would be well if Dr. Dean investigated this matter of protein determination. I believe that some of his figures are in error because of the method used. To be absolutely sure of values for the protein content of the spinal fluid, I customarily make two determinations.

I wonder if Dr. Dean has made investigations as to the effect of the other products in the spinal fluid and their relationship to the amount of protein contained in the spinal fluid?

DR. S. B. HADDEN: Dr. Dean, have you studied the relationship of the protein content to the time of onset of symptoms and the time that these studies of the total protein were made? Have you been able to attach any prognostic importance to the level of the protein? Does high spinal fluid protein usually mean a grave prognosis?

DR. JAMES S. DEAN: I appreciate Dr. Groff's and Dr. Hadden's discussions in regard to the methods of protein determinations. I spoke with Dr. Reinhold about this, and he told me that he employs the Andersch-Gibson method, which he stated has an error of only about 5 per cent. I am sorry I am not chemist enough to discuss that angle. I took 60 mg. per hundred cubic centimeters as my arbitrary upper normal value in this study, believing that this figure would allow for a possible margin of error of 20 per cent. I did not make a particular study in this paper of the influence of other products on the spinal fluid protein, except in regard to blood. When there was a gross amount of blood, the cases were omitted from the study unless the diagnosis was cerebral hemorrhage.

I did not correlate the time that the specimens were taken with the amount of protein. In the majority of cases, as I recall, the specimens were taken during the acute neurologic manifestations of the clinical condition, this being the reason for doing a lumbar puncture. I am in accord with the statement that markedly elevated protein is of grave prognostic significance in cases of infection. However,

in cases of tumors I do not know that it forecasts a particularly unfavorable prognosis, since, I believe, the location of the intracranial tumor decidedly influences the height of the protein level. Hare has pointed out that markedly elevated protein occurring in a case of tumor of the brain enhances the chances that the growth is deep lying. He did not comment on the explanation, but in the light of my hypothesis I am inclined to interpret it as meaning that a deep-lying tumor is more apt to compress the veins of Galen.

MYOTONIA DEVELOPING IN ADULT LIFE: REPORT OF A CASE. DR. BERNARD A. HIRSCHFIELD, Trenton, N. J.

Myotonia developing in adult life is exceedingly rare. According to Critchley (Critchley, M.: Disturbances of Muscle Tone, in Blumer, G.: The Practitioners Library of Medicine and Surgery, New York, D. Appleton-Century Company, Inc., 1936, vol. 9), there are less than 40 such cases on record. The disorder, usually labeled myotonia acquisita, is definitely not a familial condition and is said to occur only in men. Krabbe (*Rev. neurol.* **37**:802, 1921; *Brain* **57**:184, 1934) expressed the belief that it is actually a sequel of polyneuritis with abnormal regeneration and proliferation of the nonstriated sacrolemma fibers. However, the picture is poorly defined.

The phenomenon of myotonus itself is not understood. Lindsley and Curnen (Lindsley, D. B., and Curnen, E. C.: An Electromyographic Study of Myotonia, ARCH. NEUROL. & PSYCHIAT. **35**:253 [Feb.] 1936) made electromyographic studies which seemed to indicate that myotonus is of reflex origin, there being a persistent discharge from hyperexcitable sensory endings in the muscle. Kennedy and Wolf (Kennedy, F., and Wolf, A.: Experiments with Quinine and Prostigmin in Treatment of Myotonia and Myasthenia, ARCH. NEUROL. & PSYCHIAT. **37**:68 [Jan.] 1937) came to the conclusion that myotonia and myasthenia are both disorders at the myoneural junction, diametrically opposed, and that whereas prostigmine facilitates the action of the "vagus stuff" in myasthenia, quinine inhibits the action in myotonia. These workers found quinine as effective in treatment of myotonia as is prostigmine in management of myasthenia and regarded quinine as specific for myotonia. They gave the results of treatment in over 20 cases of myotonia, in not 1 of which did they fail to eradicate the hypertonicity (Kennedy, F., and Wolf, A.: Quinine in Myotonia and Prostigmine in Myasthenia, *J. A. M. A.* **100**:198 [Jan. 15] 1938). In their cases the condition was diagnosed as myotonia congenita or myotonia atrophica. No cases of myotonia acquisita were described.

Quinine has had no effect on the myotonus in the case presented in this report. This fact makes the case unusual if, as Kennedy and Wolf maintained, quinine is specific for this disease; it may suggest that the mechanism for disturbance in muscle tone in this patient is different from that in myotonia congenita or myotonia atrophica.

REPORT OF CASE

The patient was a white man aged 35, whose father died as the result of an accident; his mother was alive and well. He had 5 brothers and 3 sisters, all of whom were well. There was no evidence of nervous disorder in the family history. The patient had malaria in 1924, while he was in Panama; otherwise, he had always been in excellent health. He had always prided himself on his muscular strength and his powerful physique. At one time he was an amateur boxer. For the past ten years he had been a state trooper.

Toward the end of the summer of 1938 he noticed tightness in his shoulder muscles. In the course of a month this tightness, or inability to relax promptly, had involved most of the muscles of the body, sparing only those of the chest and the muscles of chewing, swallowing and expression. Coincident with this, he began to have drenching sweats, which persisted to the time of examination.

Examination.—The man looked older than his stated age of 35. General physical examination did not disclose evidence of disease of the heart, lungs, kidneys or gastrointestinal tract. The peripheral arteries, however, showed more thickening than is usual in a man of his age; this was borne out in the observation of the retinal vessels, which were definitely sclerotic. There was premature loss of hair on the head. The blood pressure was 130 systolic and 80 diastolic. The pupils responded quickly to light and in accommodation. The external ocular movements were free. The voice had a hushed, nasal quality, but the palate appeared freely mobile and there was no difficulty in deglutition. There were inconstant twitchings of the facial muscles. Otherwise, the cranial nerves functioned normally.

The patient was an extremely muscular person, showing a development which may well be called herculean. The myotonic disability was easily shown: On grasping or shaking hands there was great difficulty in releasing the hold; after utilization of the calf muscles dorsiflexion of the foot became impossible, so that he often walked on tiptoe. The myotonia was diminished after repeated attempts at movement, but soon returned after a short interval of rest. Muscular power was probably not diminished; no atrophy in the muscles had developed during the period of observation. There were constant large fascicular twitchings in all involved muscles; these were not felt by the patient. The muscles were firm, especially when they were in spasm, when they had the consistency of hard rubber. The deep reflexes were generally diminished; the abdominal reflexes were normal; there were no pathologic reflexes. There were no sensory abnormalities. Most of the time the patient was drenched with sweat.

Examination of the ocular fundi revealed elevation of the disks, with considerable angiosclerosis. A roentgenogram of the skull, however, showed no changes suggestive of increased intracranial pressure.

Results of the laboratory studies made at the Graduate Hospital were not remarkable, except for the basal metabolic rate, which, lately recorded as plus 88 per cent, had also been plus 142 and plus 153 per cent on occasion. Repeated blood counts and urinalyses were normal. The blood sugar was 96 mg., urea nitrogen 14 mg., cholesterol 185 mg., calcium 9.5 mg. and phosphorus 3.2 mg. per hundred cubic centimeters. Creatine excreted as creatinine in a twenty-four hour specimen of urine, of 850 cc., measured 282 mg. The serum phosphatase value was 7.6 Bodansky units, the total amount of inorganic phosphorus 12 mg. and the inorganic phosphorus content of the serum 4.4 mg., per hundred cubic centimeters. Biopsy of muscle tissue disclosed nothing significant.

Treatment is evidently of no avail in this case. Quinine in amounts as high as 80 grains (5.2 Gm.) a day has had no appreciable effect on the myotonus (quinine sulfate was given by mouth; a solution of quinine dihydrochloride was also given intravenously). Thyroid therapy has also been worthless. It is probably coincidental that the basal metabolic rate was lower during the period of thyroid administration. Atropine, although given in amounts which caused mydriasis and dryness of the mucosae, failed to diminish the profuse sweating noticeably.

DISCUSSION

DR. MATTHEW T. MOORE: Dr. Hirschfield has presented a case with many interesting aspects. Ordinarily, when one speaks of myotonia acquisita one thinks of myotonia occurring secondary to trauma or abnormal exposure to the elements. Many of the cases reported in the literature occurred during the World War of 1914-1918 and followed shrapnel wounds or injuries resulting from being thrown from rapidly moving vehicles. In 1935 I presented before this society a case of myotonia acquisita (Myotonia Acquisita: A Case in Which Myotonia Was Present in Both Limbs After Injury, ARCH. NEUROL. & PSYCHIAT. **35**:1393 [June] 1936). The patient showed the typical electrical reactions and clinical manifestations that one sees in myotonia.

It is interesting that Dr. Hirschfield's patient failed to respond to quinine therapy. I have under my care an athlete aged 20, whom I saw for the first time about a year ago. He presented the characteristic features of myotonia, but responded in a dramatic way to the administration of quinine dihydrochloride intravenously. Almost immediately after the injection of this substance he jumped about and stated that he had never felt his muscles could be so loose and easily brought into play. He has been on various university teams and is now on the wrestling team at college. He formerly required from twenty to twenty-five minutes of "loosening-up exercises" before he could engage in a bout. For the past year he has been free of myotonic symptoms provided he uses the prescribed 5 grains (0.325 Gm.) of quinine sulfate three times daily. As soon as he fails to take the drug there is a return of myotonic symptoms.

May I ask Dr. Hirschfield two questions? First, did this patient show the electrical reactions that one expects to find in myotonia, and, second, on what etiologic factor does he base the diagnosis of myotonia acquisita?

Dr. A. M. Ornsteen: This case is rare in itself and in the lack of response to quinine. I was interested to hear Dr. Moore say he had favorable experiences with quinine because a few persons to whom I have spoken have not been fortunate. There is a family of 3 persons with the disease in Philadelphia; all have the congenital type. None of them, the father and 2 sons, respond to quinine. The patient of Dr. Hirschfield's and others with acquired myotonia that I have seen also failed to respond to quinine. The work of Kennedy and Wolf, while admirable from its philosophic point of view, seems to me to contain much that must be proved with regard to the diametrically opposed conditions of myotonia and myasthenia gravis.

There are many reasons why one would not expect quinine to give relief; certainly, in a fair percentage of cases it does not seem to be effective. This case of Dr. Hirschfield's would pass anywhere for a classic instance of myotonia, presenting all the reactions, including the electrical and no one would have difficulty in making a diagnosis of myotonia without the history.

Dr. Bernard A. Hirschfield: First, I am not certain about the diagnosis of myotonia acquisita. From the literature, it is difficult to obtain a definition of myotonia acquisita. The fact that this condition came on abruptly so late in life in a person with a negative family history made me lean to that diagnosis. However, as I stated, the premature baldness, the fact that the patient looks a great deal older than he says he is, the sweating and the fascicular tremors may eventually put this case in the class of the dystrophic myotonias. I cannot explain the failure of the action of quinine here, but it is a fact. I have certainly given the patient enough quinine to make sure. He is very tolerant to quinine; he has had more than 80 grains a day without any buzzing in the ears.

I agree that I have not been able to obtain an accurate basal metabolic rate, for it is impossible to get this man to relax. I have never seen him when there was not considerable spasm. The metabolic rate, therefore, represents one of active exercise.

J. C. Yaskin, M.D., *President, in the Chair*

Regular Meeting, May 26, 1939

Neuralgic Headache and Facial Pain. Dr. Samuel B. Hadden.

There is little in neurologic literature on the symptomatology or management of occipital neuralgia, and the only reference in textbooks is a brief statement that at times the occipital nerves may be the site of neuralgic pain.

At the point where the occipital nerves penetrate the tendinous portion of the trapezius muscle they are prone to become involved in chronic inflammatory lesions, such as fibrositis, and, as a result of involvement at this point, pain may be referred to any portion of their distribution.

Symptomatology.—Occipital neuralgias may be divided into three groups—acute, intermittent and chronic. The symptoms vary, depending on whether the lesser or the greater branch is involved. In the acute attack the onset is sudden and occurs frequently after sudden movement of the head or as a result of exposure to wind and cold. The first symptom is usually a sharp suboccipital pain of a boring character. The pain spreads anteriorly to the temporal area, and frequently into the retro-orbital region. There are retraction of the neck and elevation of the shoulder on the side involved, and occasionally the patient complains of photophobia. In some extremely severe forms there are vomiting, pallor and profuse perspiration. Because of the suddenness of onset and severity of symptoms, such conditions are often regarded as spontaneous subarachnoid hemorrhages. Such a headache may last for several hours, despite the use of analgesics, and when it subsides residual soreness of the scalp is noted. During the acute attack pressure over the greater or lesser occipital nerve produces exquisite pain. Hyperesthesia in the distribution of the nerve is usually noted, and tenderness over the carotid arteries is frequently present.

The intermittent type is characterized by periodic headaches resembling the acute form just described, with freedom from pain between the attacks. The paroxysms may be precipitated by exertion, fatigue, wind, cold, damp weather or low barometric pressure. The objective symptoms of tenderness over the nerves at their point of exit, the hyperesthesia and the tenderness over the carotid arteries are usually constant. In addition, tenderness at the upper margin of the trapezius muscle is usually noted, the occiput is rotated to the side involved, the head is slightly retracted and the shoulder elevated. If the exacerbations are acute the diagnosis is usually that of migraine, and in cases in which the pain extends into the supraorbital and retro-orbital areas neuralgia of the first branch of the trifacial nerve is usually considered.

In cases of the chronic type pain and tenderness are almost constantly present in the occipital and temporal regions. The pain tends to be worse at night. In these cases acute exacerbations are uncommon, the patient usually stating that the headache is constant. As a result of tenderness of the scalp, there is a tendency for patients to wear their hats tilted away from the side involved, since any pressure on the scalp aggravates the pain. Frequently, soreness of the scalp is apparent as the hair is combed.

The intermittent and chronic types may be present for many years, with ordinary treatment and medication affording little relief. From the description of the symptoms it is easily understood how in most cases the intermittent and chronic varieties have been regarded as migraine, but administration of ergotamine tartrate and other measures, usually of benefit in migraine, are of little help. In many cases the headache has been regarded as of sinus origin, and intranasal operation has often been used in an effort to give relief. In cases in which the principal pain is in the supraorbital and retro-orbital region, tic douloreux has usually been considered to be the cause. In an occasional case the soreness and pain occur in the malar region and in the teeth and upper jaw. Intranasal soreness and pain have also been observed in a few cases.

Etiology.—In many cases infection of a paranasal sinus previously existed, or at least was believed to exist, and in a few instances such infection was still obvious. Infection of the paranasal sinuses seems to be one of the principal predisposing causes, but the neuralgic headache may continue long after all evidence of such infection has ceased to exist. Other foci of infection tend to play a role, and in the cases of infectious origin other neuritic manifestations are frequently present, especially the abdominal-intercostal neuralgia described by Carnett.

Many of the patients observed have had evidence of cervical arthritis or arthritis elsewhere, and postural defects also appear to be an etiologic factor. In such cases the shoulder on the side involved is usually high and the sternocleidomastoid muscle on that side is contracted, with resulting rotation of the occiput downward and to the side of involvement.

I have observed a large number of cases in police officers and firemen who wear a heavy uniform cap. Pressure due to a tight or heavy hat seems to be a factor. Wearing of tight bands about the head by nuns also appears to produce this variety of headache. It is possible that the ischemia produced by the constricting band is the mechanism responsible.

In 1 case the type of hair dress seemed to be the important factor, since changing the style of dressing the hair gave immediate and complete relief. This patient was a professional dancer. She parted her hair in the middle and made two plaits, which she crossed in the back and then pulled tightly forward, encircling her head.

Trauma to the head accounts for a large number of such headaches. As a result of a blow on the vertex, with the consequent hematoma, the blood tends to gravitate down through the areolar tissue of the scalp and appears to become arrested in the suboccipital region and to set up nerve irritation. In most cases in which trauma is the cause the headache is chronic, although many are of the intermittent type.

Conditions in which the pain is confined to the accepted distribution of the occipital nerves are easily understood, but it is difficult to explain the pain which occurs in the supraorbital division, and occasionally in the second division, of the fifth cranial nerve. It is possible that Sherrington's theory of overlapping explains these cases. In recent work Loewy has pointed out that the area of overlapping of the trigeminal and the cervical nerve distribution is far greater than is generally accepted. Head's theory does not seem adequate, for it is rare that in cases of trigeminal neuralgia there is overflow into the cervical distribution. The mechanism of stimulation of sensory nerve endings is not fully understood, but it is believed to be chemical. It is possible therefore that in cases in which the pathologic lesion appears to be in the suboccipital region antidromic impulses may be responsible for the release of the chemical substance necessary for stimulation of sensory nerve endings and that this excess of chemical substance may then stimulate the endings of the trifacial nerve which overlap in the scalp, with resulting pain in the facial area.

Treatment.—Many patients have discovered that the only method of obtaining relief from the headache is by pressure over the tender point at the exit of the greater or lesser occipital nerve. Some have obtained slight relief from the application of an ice pack; as a rule, however, this tends to aggravate the discomfort, and heat is more effective.

Massage at the site of suboccipital tenderness sometimes proves helpful. The most effective form of heat is infra-red radiation; this combined with massage gives relief in a large percentage of cases.

In all probability, it is the form relieved by heat which is referred to in English medical literature as the rheumatic type of headache. Recently, Cyriax called attention to a rheumatic type of headache associated with painful nodules in the scalp. I have never seen a case in which these nodules were present. Yawger, in describing a case of similar headache, also advised heat and massage.

The most effective treatment has been infiltration of the perineural tissue at the site of tenderness with procaine hydrochloride or alcohol. Anesthesia of the posterior portion of the scalp quickly follows effective injection, and many times complete anesthesia to pinprick extends far beyond the accepted area of distribution of the occipital nerves into the area of supraorbital distribution. Strangely, in several cases one or two injections of procaine hydrochloride have been effective in giving relief from headache for several years, without recurrence to date.

Summary.—A symptom complex due to neuralgia of the occipital nerves has been presented in which sharp, unilateral headache occurs, beginning in the suboccipital region and radiating anteriorly into the supraorbital division of the fifth cranial nerve. The outstanding objective signs are tenderness over the occipital

nerve at the point of exit in the neck, retraction of the head to the affected side and tenderness over the carotid vessels. The symptom complex is most frequently confused with migraine and tic douloureux involving the first division of the fifth cranial nerve. Relief is afforded by heat, massage and injection of a solution of procaine hydrochloride or of alcohol into the nerve.

DISCUSSION

DR. ROBERT A. MATTHEWS: Dr. Hadden's paper is of considerable value because it offers a method of approach to the understanding of a troublesome and little understood type of headache. Dr. Hadden did not comment on any personality characteristics that these patients may have shown. It is known that occipital headache is one of the most common complaints of neurotic persons, although it is not usually unilateral. It would be interesting to know how many of the patients exhibited psychoneurotic tendencies.

This also raises a question of the cause of occipital headache in the psychoneurotic patient, with the complaint of tenseness and stiffness in the neck. It has occurred to me that if the neurotic patient has generalized muscular hypertonia, involving the muscles of the neck, especially since the neck cannot be readily relaxed during the day and the head must be held upright, the constant tension may result in compression and irritation of the occipital nerves at the point where they penetrate the muscles. The treatment suggested should afford symptomatic relief in such cases, although there may be danger of fixing the neurosis on a physical basis. Dr. Hadden has treated many policemen, but one knows that neurosis is not unusual in officers of the law.

DR. D. J. MCCARTHY: The occipital neuralgia referred to as the neurotic rheumatic type, with the nodules at the base of the occipital area, has been a common type described by all British neurologists; in my experience it is a frequent form of the occipital neuralgias. Treatment has consisted of heat and massage; usually the results were favorable.

Either the "overflow" neuralgias are rheumatic, or there is a focus of infection in the sinus area; however, that is related to the so-called nodular type of occipital neuralgia.

How does Dr. Hadden explain the tenderness?

DR. SAMUEL B. HADDEN: In answer to Dr. Matthews, in managing this series of patients, the psychoneurotic element, naturally, was evaluated, although it could not always be ruled out. One of the criteria used to determine whether the patient had occipital neuralgia was the definite localization of the point of tenderness over the anatomic exit of either the lesser or the greater occipital nerve; pressure over other portions of the scalp failed to give any appreciable amount of tenderness. Psychoneurotic patients are not likely to describe symptoms on such a definite anatomic basis.

Dr. Matthews' point that hypertonia is present in psychoneurotic patients is well taken; I am certain that in most cases of this group, as a result of pain, hypertonus of the muscles of the back of the neck and in the upper scapular and interscapular regions was present in all or most instances. I can verify the statement about patrolmen, and I am sure that in persons of that type relief by any method, even injection of an analgesic into the scalp, could not be produced so consistently if the symptoms were purely neurotic.

Dr. McCarthy's description of the rheumatic type of headache is well recognized, but I have seen no reference to the overflow into the distribution of the first division of the fifth nerve in cases of this type; it was that particular phase of the problem in which I was especially interested, for some of the patients had had surgical intervention without particular relief; in this group may be included some of the pseudoneurotic patients who are not relieved by ordinary measures designed for the relief of trifacial neuralgia.

CEREBRAL COMPLICATIONS OF SURGICAL OPERATIONS: A CLINICOPATHOLOGIC STUDY. DR. H. E. RIGGS and DR. ALBERT BEHREND.

One of the most distressing complications of surgical operation is the appearance of symptoms of involvement of the nervous system. The clinical manifestations of such involvement are frequently so protean that their relation to the surgical procedure and the anesthesia is not always apparent. Yet knowledge of the mechanism by which the clinical symptoms are produced is essential for their treatment. We wish to show that cerebral complications of any type encountered after surgical operation may be produced by relative cerebral anoxia, resulting from acute general circulatory collapse, precipitated by the anesthesia, in persons whose margin of neurocirculatory reserve has been reduced by masked chronic circulatory insufficiency.

Type of Material.—The 21 cases comprising the material for this study were collected from the several surgical services of the Philadelphia General Hospital. Preoperatively, only 6 patients (28 per cent) could be considered as poor anesthetic risks. These included 4 patients with amputation at the midthigh for gangrene, 1 with splenectomy for hemolytic anemia and 1 with an exploratory laparotomy for intestinal obstruction. The average age was 38 years, and only 4 patients (19 per cent) were over 50.

Operations.—These included celiotomy, operations on the femur, obstetric anesthesia, dilation and evacuation of the uterus and incision of a paronychia. The anesthetic agents were ether, cyclopropane, nitrogen monoxide and procaine hydrochloride (spinal anesthesia).

Symptoms.—In our cases symptoms usually suggested diffuse involvement of the entire brain; they included sudden death on the operating table, prolonged coma (twelve to twenty-four hours), psychic disturbances, generalized convulsions and signs of focal cerebral lesions (paralysis). Four patients with symptoms in the last group were under 33 years of age; the fifth (61 years of age) had shown transient weakness of the right side for nine days prior to operation, with complete motor paralysis developing within twenty-four hours after the operation. In all our cases, at some period, more than one symptom was present. Hyperpyrexia might also be mentioned as a symptom of cerebral involvement in these cases. A progressively increasing elevation of temperature unexplainable on an infectious basis, was present in 76 per cent of the patients who survived longer than twelve hours.

Pathologic Picture.—Regardless of the clinical manifestations, the brain showed widespread cellular damage. When the patient survived less than two days there was little evidence of glial reaction. Eighty per cent of the patients living longer than forty-eight hours presented focal areas of astrocytic proliferation and phagocytic activity suggesting beginning repair and scar formation. The intensity of the degenerative changes in the more vulnerable areas of the brain, as well as the diffuseness of the process, pointed to a period of relative anoxia as the etiologic factor. However, study of the cerebral capillary bed showed that the cellular degeneration was not due to a direct and selective effect of anesthesia on brain cells.

The presence of perivascular and pericellular edema demonstrated that the anoxic changes were secondary to alterations in the permeability of the capillary wall. Further, edema and congestion of the visceral organs showed that the alteration in the cerebral capillary bed was merely a reflection of generalized capillary damage. Such changes suggest that the degeneration in the brain was merely a part of the picture of generalized circulatory insufficiency in these cases. The damage due to such acute general circulatory stasis would be most severe in the brain as the result of the effect of the closed box of the skull on the increased volume of the edematous brain, and of the high metabolic rate and oxygen requirements of neural tissue. Clinically, the evidence of cerebral dysfunction is usually so dominant that accompanying signs of disordered visceral function are obscured or overlooked.

Role of the Anesthetic Agent.—While, in our series, histologic study suggests that death resulted from generalized circulatory insufficiency, in which cerebral symptoms dominated the clinical picture, it seems unlikely in the light of present knowledge that anesthesia was the sole causative agent. In no case was the period of anesthesia unusually long. Three patients were operated on under very light, brief anesthesia induced with nitrogen monoxide, and in 2 cases spinal anesthesia alone was employed. Temporary cardiac or respiratory embarrassment during operation occurred in only 2 of the 21 cases. However, experimental work suggests that any form of anesthesia may contribute to cerebral anoxia through its action on the general circulation. The fall in blood pressure during spinal anesthesia is evidence of the effect of this form of anesthesia on circulatory efficiency. A marked drop in cardiac output with a fall in blood pressure during ether anesthesia has recently been demonstrated, as have the presence of hemoconcentration and loss of circulating blood volume. With the same anesthetic agent, the liver shows a marked decrease in functional activity. In fact, from recent work it is concluded that all anesthetic gases in concentrations necessary for deep surgical anesthesia function, at least in part, through the anoxia they produce.

Such alterations in circulation are usually transient, and in laboratory animals complete anesthesia in itself is rarely sufficient to produce failure of the circulation. However, experience during the World War demonstrated that anesthesia may precipitate circulatory collapse (shock) under conditions in which the circulation is already impaired. In other words, when prior to operation an oxygen deficit, due to impaired blood flow, is present, the transient and relative anoxia of anesthesia may precipitate failure of the circulation.

Factor of Latent Cardiocirculatory Insufficiency.—Preoperative studies in our cases gave no clinical indication of cardiocirculatory decompensation; yet structural alterations in the cardiovascular system were observed post mortem in all cases. Although no signs of peripheral circulatory insufficiency were noted clinically, in 9 cases of young persons who died within twenty-four hours of operation the brain showed cumulative progressive degenerative changes. Such changes were interpreted as the effects of circulatory insufficiency existing prior to the period of surgical anesthesia.

Staining Technic.—The trichrome stain used in the slides shown is a method developed by Miss Edna Beyer, technical assistant in neuropathology at the Philadelphia General Hospital. Connective tissue, collagen and mucus stain blue. Muscle and brain tissue stain red, but become progressively basophilic when degenerative changes are present.

Throughout the brain blood vessels showed degeneration of the muscular coat, with accumulation of fibrous and hyaline connective tissue in the media and the adventitia and in the perivascular spaces. Excessive amounts of connective tissue were also present in the subarachnoid space. Extensive degeneration changes were present in the myelin sheaths throughout the brain. This demyelination was most marked around the blood vessels and in the cerebral vegetative centers. The presence of changes of a similar nature (parenchymatous degeneration and increased connective tissue stroma) in the visceral organs demonstrated that the circulatory insufficiency was general rather than localized to the cerebral vascular tree. However, the greater functional dependence of the brain on circulatory integrity, as well as the frequent anomalous formation of the circle of Willis, may well have intensified locally the effects of the general circulatory insufficiency.

Under ordinary circumstances, such circulatory insufficiency would be adequately compensated, but, as shown by degenerative changes in the brain, the margin of neurocirculatory reserve would be reduced. As a result, the added stress of anesthesia and the acute surgical condition would be sufficient to precipitate a generalized circulatory collapse, clinically manifested by symptoms of cerebral dysfunction.

Conclusions.—1. Cerebral complications of surgical operation may result from diffuse degenerative changes in the brain, incident to generalized circulatory collapse.

2. Such circulatory collapse may be precipitated by the anesthesia in cases in which there has been chronic latent cardiocirculatory insufficiency.

DISCUSSION

DR. F. C. GRANT: I have been much interested in this report of Dr. Riggs; recently work has been done in the Harrison laboratory by Dr. L. M. Weinberger, of the staff of the University of Pennsylvania Hospital, on the effect of complete anoxemia of the brain produced by entirely cutting off the blood supply through temporary ligation of the pulmonary artery in cats. As a result of this study, it was found that if the blood supply of the brain was cut off for not over three and a half minutes the animal survived. The blood supply was so completely shut off that when the retinal vessels were examined the arteries and veins had entirely disappeared. The time at which they reappeared was taken as the point at which the circulation was reestablished. Some of the animals recovered after seven and a half minutes of complete anoxemia. The latter animals, however, were entirely blind, deaf and paralyzed, and did not survive long. While anoxemia of the brain is unquestionably important in causing the death of patients undergoing operation, one wonders whether there may not be some factor other than the cerebral complication, for it seems extremely unlikely that the blood supply of the brain could be cut off for any length of time comparable with that in the experiments on animals in which recovery is complete. I wish to ask whether there is any explanation for the operative disasters other than possible cerebral anoxemia.

DR. L. M. WEINBERGER: Dr. Riggs has brought up an important subject. I wish to ask her one question: If one supposes that the premorbid changes in the brain she described play a large part in the ultimate effects of the anoxia, one would expect that, on a priori grounds at least, the older the patient and the more vascular disease is present the higher would be the incidence of postoperative cerebral disturbance. On the contrary, I found in an analysis of 230 cases that the greatest number of the patients fell into the younger age group; 40 per cent were under the age of 20 and 58 per cent under the age of 30. If the vascular changes that were shown in the slides are responsible, even in large part, for the susceptibility of the brain to asphyxia it seems that the older the patient the more likely would cerebral accidents occur, but that is not the case. That such accidents tend to occur in young persons may be due to the fact that their basal metabolic rates, and therefore their oxygen requirements, are so much higher than those of older persons. It is known that the caloric output of children is about 53 to 54 calories per minute, and that for a person aged 16 it is only 38 calories.

Dr. Riggs spoke of the pathologic changes shown by the patient who died on the operating table. In all studies on the effects of cutting off the blood supply to the nervous system, workers have agreed that it requires a period of post-asphyxial or postanoxic survival for neuropathologic alterations to occur. From three to six hours must elapse before observable pathlogic changes appear.

DR. M. W. THORNER: The matter of the type of anesthetic must be considered and should make one cautious about interpreting all the changes as due to anoxia. In certain cases of anesthesia induced by sodium amytal it has been shown that the oxygen uptake of the brain was 50 per cent or less of that under normal circumstances.

When an organ is deprived of circulating blood, as well as of oxygen, the flow of ions and of dextrose into the region is stopped. It would be just as reasonable to say that the organ is not obtaining its normal supply of calcium and other chemicals and to stress that point.

DR. A. SILVERSTEIN: From the Mayo Clinic, in 1922, there was reported a series of 20 cases of postoperative shock which was found to be due to fat embolism. In 2 of the cases that Dr. Riggs reported the cerebral disturbances followed orthopedic manipulation and amputation, respectively. Fat embolism is known to result at times from such procedures. As to the anesthetic in these cases: Raymond and Moore have demonstrated dramatically that the injection of ether or histamine can change the emulsified fat normally present in the blood into embolic fat in amounts sufficient to produce embolism throughout the circulation. Cerebral fat embolism is more apt to occur in young persons, especially in those who have strong cardiac structures and in those who have some condition that will cause forceful contraction of the heart.

DR. H. E. RIGGS: As to Dr. Grant's question about anoxia occurring only in the brain: I do not believe that that is possible. Cerebral anoxia is predominant for the reasons I gave, namely, the effect on the brain of swelling due to circulatory status and the higher amount of oxygen needed by brain tissue; we have always observed changes in other organs. Dr. Behrend, who is doing the clinical work, hopes to show that there is circulatory failure in all tissue.

In 2 cases we have had good results by increasing circulatory efficiency. We think that if the hemoconcentration can be overcome and the general circulatory factor improved the cerebral symptoms will take care of themselves.

Dr. Weinberger's questions are hard to answer. I agree that these accidents have appeared to occur more frequently in younger persons, but I deliberately selected young people with no obvious clinical complications. On the other hand, I do not believe that one can judge from chronologic age alone; the biologic age must be considered. Such patients may be only 6 years of age, but their brains are the brains of old persons. I refer Dr. Weinberger to Dr. Cherniack's work, in which changes are demonstrated as early as six minutes after reduction of oxygen in the atmosphere. The study of cells alone will not give any help. One must be guided by other changes, such as the edema that is present around the cells, and one must be careful that this has not occurred post mortem. Dr. Cherniack's animals were killed instantly. The results in those treated with atmosphere deficient in oxygen are striking to see. This has been described in his monograph published by the United States Department of Commerce, Bureau of Mines. One cannot tell whether there is anoxia unless one looks at the entire brain and observes the distribution of the changes.

I cannot say much about fat embolism. I stained all these specimens with a fat stain and found plenty of fat in all the vessels, but I have thought it was part of the hemoconcentration. I admit that this is simply a personal opinion, but it has been demonstrated by others.

TREATMENT OF MULTIPLE SCLEROSIS WITH NICOTINIC ACID AND VITAMIN B_1: PRELIMINARY REPORT. DR. MATTHEW T. MOORE.

Many hypotheses have been advanced regarding the cause of multiple sclerosis, and their variety and uncertainty are reflected in the forms of treatment which have been used. Recently, emphasis has been laid on the possible etiologic implications of vascular changes and the therapeutic employment of fever therapy to promote hyperemia and an increased flow of blood in nerve tissue. The application of fever therapy in its various forms has many annoying disadvantages, and indeed dangers, which should make welcome a less disturbing method of inducing the changes wrought by this treatment.

Smith, Ruffin and Smith reported the successful treatment of pellagra with nicotinic acid and described the reaction following the intramuscular administration of 60 mg. of nicotinic acid: "A marked flushing of the face, neck, chest and arms appeared a few minutes after intramuscular injection and lasted fifteen minutes." The mention of marked flushing of the skin led me to consider the

feasibility and advisability of using nicotinic acid in cases of multiple sclerosis and to attempt to determine whether the cerebrospinal nervous system becomes hyperemic in a manner similar to that observed in the skin. If the answer to this query is in the affirmative, some of the beneficial effects of fever therapy might be realized by the use of this substance and the baneful side effects be eliminated.

The 5 cases reported here represent, in the main, advanced multiple sclerosis. Nicotinic acid therapy was begun in the first case on Feb. 15, 1938, and has been used almost continuously, with a few interruptions, up to the present. Prior to the use of nicotinic acid and vitamin B_1, these patients received in the aggregate the following forms of treatment: quinine bisulfate, germanin (reported to be a sodium salt of sym. bis. [*m*-aminobenzoyl-*m*-amino-*p*-methylbenzoyl-*l*-naphthylamino-4,6,8-trisulfonic acid] urea), a high vitamin diet, hyperpyrexia (induced by typhoid vaccine intravenously, diathermy and the Kettering hypertherm), forced cerebrospinal fluid drainage and histidine monohydrochloride.

Nicotinic acid, when given in proper doses intravenously or intramuscularly, produced vasodilatation of the skin of the face, neck, chest and extremities, as was observed by Smith, Ruffin and Smith, and subsequently by others. In view of the pathologic changes of multiple sclerosis centering in the spinal cord and brain, the goal of therapy is to alter or to arrest, if possible, the progress of existing reversible pathologic processes in these tissues.

The evidence presented in this paper that nicotinic acid produces vasodilatation and increased flow of blood in the brain and spinal cord is based on the rise of cerebrospinal fluid pressure during the period of flushing of the skin and the photographic visualization of dilated vessels and increased capillary filling in the brain and spinal cord of the cat.

The favorable results obtained in the cases reported may be due in part to the increased oxidation and nutrition of the brain and spinal cord brought about by the improved blood supply. Whether the salutary effect of nicotinic acid is due solely to its effect on the vasculature of the brain and spinal cord or to the possible additional role of nicotinic acid as a vitamin cannot be answered with any degree of certainty within the scope of this paper.

Deprivation of vitamin B_1 results in a disturbance in the normal combustion of carbohydrates and the accumulation of pyruvic acid in the nervous system; both these deviations from the normal produce significant physiologic and pathologic changes in nerve tissue, and replenishing of vitamin B_1 restores the ability of the nervous system to handle properly pyruvic acid and dextrose.

Vitamin B_1 was used in conjunction with nicotinic acid in this series of cases, admittedly on an empiric basis. It was thought that whatever effect thiamin chloride may have on diseased nerve tissues, in the light of the foregoing presentation, its effect would be enhanced if it was active at the time vasodilatation and improved blood supply were operative during the action of nicotinic acid.

In every instance in this series of cases in which nicotinic acid–vitamin B_1 therapy had been halted for a period there was return of incapacitation, spasticity and incoordination. The patients have been the severest judges concerning the relief they experienced from the drugs, and in every case have requested return to their use after cessation of treatment for a short time.

To be sure, complete remissions have not been achieved by the use of nicotinic acid and vitamin B_1 in the cases reported; on the other hand, these cases represented advanced multiple sclerosis in which many forms of therapy had been used without appreciably arresting the progress of the disease, and in 2 cases previous treatment had aggravated the condition. Every patient noticed improvement in bodily movements and in walking. The patient in case 2 has regained her aptitude at the piano and has lost the annoying paresthesias. The patient in case 4 is now able to stand and has overcome much of his terrific spasticity. The patient in case 5 is no longer bedridden and can move his legs, stand while assisted and use his arms, which were previously powerless, for purposes of dressing and

eating. It is evident, therefore, that some improvement has resulted and, what is more significant, that the previous downward course of the illness has been arrested.

What effect nicotinic acid–vitamin B_1 therapy may have in cases of early multiple sclerosis is still to be determined. Further investigation in such cases with both nicotinic acid and vitamin B_1, using other modes of administration and other doses, may yield more encouraging results, and perhaps throw light on the many blindspots in the subject of multiple sclerosis.

This paper was published in full in the January 1940 issue of the *Archives of Internal Medicine*, page 1.

DISCUSSION

DR. J. C. YASKIN: Several thoughts occur in connection with a presentation of this sort. First, there are two diseases treatment of which is notoriously difficult to evaluate—Parkinson's disease and multiple sclerosis. Second, one knows that multiple sclerosis does have remissions, even when well advanced. Third, a great many patients with multiple sclerosis are easily influenced by suggestion; especially is this true of Dr. Moore's second patient, whom, I believe, I saw in the Orthopaedic Hospital. Fourth, some have been using vitamin B_1 in treatment of multiple sclerosis. As a matter of fact, the routine is, when possible, to give fever therapy with the hope that the disease is of virus origin and that some of the organisms may be killed. After this, quinine, liver, liver extract and wine are given when the patients can afford these agents, and I can assure Dr. Moore that a number of patients have shown considerable improvement when they have taken vitamin B_1 and liver. Last, although Dr. Moore had 1 patient under his observation only a few months, it is a year from the time of beginning the treatment. Although it is difficult to evaluate results, all in all, any one who can suggest something useful in the treatment of multiple sclerosis deserves a great deal of credit.

DR. MICHAEL SCOTT: I was much interested in Dr. Moore's experimental work with nicotinic acid. It was given to 1 patient at Temple University Hospital while on the operating table, and the exposed brain was observed. I did not see any change; however, that was in only 1 case, and only part of the temporal lobe was exposed.

DR. A. SILVERSTEIN: Dr. Moore's second patient, I think, went the rounds of every neurologist in Philadelphia. I saw him years ago; he had early signs of multiple sclerosis, but there was such a marked psychogenic overlay that the question of hysteria was considered. He was highly suggestible, and still is. He is now at the Philadelphia Home for Incurables, and is absolutely disabled. If one asks him how he is getting along, he says: "I feel fine, as long as I get that injection in me." On the day on which he does not receive an injection he feels sick. I have never seen the man stand. He still has severe spasticity; it all depends on what one means by making a person better. As far as he is concerned, he is disabled. Aside from the upper extremities, he is a cripple. I have seen 4 patients who have objected rather strenuously to this treatment.

DR. A. ORNSTEEN: Does Dr. Moore think that the response is due entirely to vasodilatation, to the exclusion of the replacement therapy of avitaminosis?

DR. MATTHEW T. MOORE: I realize fully that in bringing forth any new form of therapy of multiple sclerosis I am embarking on a stormy sea. However, any method or procedure that promises the slightest step forward in treatment of this particularly distressing disease will be of value.

As regards remissions in multiple sclerosis: Many patients do show remissions, but the recent article by Brown and Putnam (Remissions in Multiple Sclerosis, ARCH. NEUROL. & PSYCHIAT. **41**:913 [May] 1939) showed clearly, I believe, the statistical evidence regarding remissions and the type of cases in which the remissions occur. They stated that in cases in which the lesions are

small, producing such symptoms as diplopia, the probability of remissions is greater and the duration of the remission longer; in cases in which the lesions are large, producing paraplegias and advanced pathologic reflexes, the hope of remission is slight. The part played by suggestion I have, of course, taken into consideration. Any patient with a distressing disease, such as multiple sclerosis, in which the outlook is hopeless is always amenable to wishful thinking, to any hope that can be held out to him, and therefore is highly suggestible.

As I indicated by the lantern slide illustrations, nicotinic acid was used because I believed that if hyperemia similar to that in the skin could be brought about in the nervous system one could dispense with fever therapy and its deleterious effects on nerve tissue. Bennett, Hartman and others have shown that definite pathologic changes may occur in the brain and spinal cord as the result of fever therapy.

The statement that multiple sclerosis may be of virus origin is open to serious question. Pathologically, it is a degenerative disease from the start. As regards the end results in this series: I have been using this therapy for a year and three months in 2 cases and for a year in the remaining 3 cases; in the first 2 cases the improvement has been encouraging, despite the advanced stage of the disease in both.

In reply to Dr. Scott regarding the appearance of the brain after the injection of nicotinic acid: The "pinking" of the cerebral cortex is more or less determined by the dose of nicotinic acid. In man, unless 60 mg. of nicotinic acid is given as a minimum dose, there may not be any appreciable response.

None of the patients noted a favorable response in less than a week. The spasticity never decreased immediately. The diminution in spasticity was of a subjective character first. There was diminution in spasticity that could be observed objectively later; that this was not due to suggestion was simply shown in case 1 and in case 5, which I did not describe, that of a man who was absolutely bedridden and had not been able to move his body or lower limbs for six months. In two weeks he was able to move his toes, and in three months to undress himself. As regards the mental reaction of the second patient, mentioned by Dr. Silverstein, it is true he was suggestible. This man had the most advanced multiple sclerosis I have seen, with pronounced spasticity—so extreme that I was afraid he had a tumor of the cord extending upward into the foramen magnum; however, careful studies eliminated this possibility. This patient was admitted with extreme spasticity and crossing of the legs. He can now uncross his legs voluntarily and is able to move in bed, which he formerly could not do.

As to Dr. Ornsteen's question regarding vasodilatation versus replacement therapy: I have used nicotinic acid on the basis of the effects of vasodilatation, increased oxidation and improved nutrition, which appear concomitantly with increased blood flow in the nervous system. As far as the replacement therapy is concerned, one knows that vitamin B_1 unquestionably plays a role in the degenerative neuropathies; for that reason, the two drugs were used simultaneously to obtain a complementary effect.

NEUROLOGIC ASPECTS OF THE OPTIC NERVE. DR. GLENN G. GIBSON (by invitation).

Various lesions of the optic nerve were described with lantern slides of photographs of the fundus. The normal optic disk and its anatomic variations were described. The differential features of medullated nerve fibers and structurally full disks were discussed and differentiated from the various disturbances which occur in this area. Pallor of the optic disk was described and differentiated from atrophy of the optic nerve, and the clinical significance of this differentiation was stressed. The various forms of edema of the optic nerve were demonstrated, discussed and differentiated. Optic neuritis and choked disk were differentiated in their acute and chronic stages. The neurologic, medical and ophthalmologic aspects of these problems were discussed.

PINEALOMA: CLINICOPATHOLOGIC STUDY, WITH REPORT OF A CASE. DR. M. S. HWANG, DR. M. W. THORNER and DR. J. C. YASKIN (by invitation).

In the past decade, psychiatrists have become interested in psychosomatic relationships and neurologists have attempted to correlate somatic, vegetative, metabolic, endocrine and psychologic disturbances in terms of neurophysiology. The chief battleground for localization of the majority of these functions is at present in the region of the hypothalamus. Any clinicopathologic material which contributes to an understanding of this region is worth reporting. It is for this reason that the following case is presented.

REPORT OF CASE

A boy aged 8 years had polyuria and polydipsia, followed two years later by periods of somnolence, excitability, irritability and precocious sexual interests. At the age of 11 he had macrogenitosomia praecox and left hemiparesis. At the age of 12 he exhibited optic atrophy, inferior quadrantic homonymous hemianopia, premature closure of epiphyses, a low metabolic rate and increase in estrogen and in the gonadotropic principle. There was no evidence of increased intracranial pressure and encephaloventriculographic findings were normal. At 13 he had febrile attacks and some papilledema. Autopsy revealed a pinealoma extending through the third and the right lateral ventricle and the base of the brain.

In attempting to make a clinicopathologic correlation, the case was discussed from the standpoint of diabetes insipidus, pubertas praecox, visual disturbances, personality changes, somnolence and recurrence of fever. While no definite conclusions can be drawn, it appears that the lesion in this case, from its inception, exerted most of its influence on the hypothalamus and the adjacent optic chiasm, without, however, producing increased intracranial pressure. The possible implications of the endocrine abnormalities were briefly discussed.

DISCUSSION

DR. C. W. DUNN: I recall a girl with pubertas praecox, treated at the Graduate Hospital, who had increased intracranial pressure and on whom Dr. Francis Grant, after roentgen therapy in the early phase, when the condition was not as evident, performed an exploratory operation. The child was then about 10½ years of age. She had menstruated and shown pubic hair at the age of 18 months, and there had been general precocious development. An intrasellar cyst was observed.

DR. J. C. YASKIN: Dr. Dunn has observed a case of pubertas praecox associated with an intrasellar tumor or cyst. In a search of the literature, I have not found a case associated with a tumor of the pituitary gland or with one in that region. Tumors in the region of the third ventricle do not give rise to pubertas praecox. The disturbance does occur with diseases of the pineal gland. I may be wrong with regard to the pituitary tumor, but I have not found a case in which it was associated with pubertas praecox.

CHICAGO NEUROLOGICAL SOCIETY

VICTOR E. GONDA, M.D., *President, in the Chair*

Regular Meeting, April 20, 1939

STUDIES ON FAMILIAL PERIODIC PARALYSIS. DR. MELVIN F. BLAUROCK (by invitation).

This rare condition has become of extreme interest to my co-worker, Mrs. Whitcomb, and me, but because it is not common and is seldom seen in private practice, I shall not produce an abundance of charts and statistics. The purpose

of this paper is to present the high lights of our research. The present case was first diagnosed as one of familial periodic paralysis by Dr. Alfred Solomon in November 1936.

W. P., a man aged 23, had his first attack of paralysis at the age of 14. At that time he was unable to move any part of his body except his head. He first noticed the paralysis when he awoke at 6 a. m. By evening he was able to be up and around, but was still very weak. We have observed that the flaccid paralysis involves all voluntary muscles except those of the head and neck and the muscles of respiration. During a severe attack the muscles of mastication and expression and of the neck are also involved. There have been a few very severe attacks in which respiration was difficult.

The spontaneous attacks invariably occur during the night, usually between 1 and 3 a. m., and last from four to forty-eight hours. Between attacks the patient is active and feels perfectly well. The longer the period between attacks the stronger he feels. The interval between attacks, without medication, has varied from a day to a month or more. He has observed that he is more apt to have an attack after a large meal, after reading a great deal or during changeable weather, especially on rainy days. Often he can foretell an attack from a feeling of fatigue which appears the evening before the paralysis develops.

During an attack he is depressed, irritable and somewhat uncooperative and complains of headache, anorexia, nausea and various muscular pains. He does not have any pain if he is frequently turned and massaged.

In a severe attack the pupils are dilated; the heart rate is slow, and a rough systolic murmur is heard at the apex. The skin is cool, and the extremities are apt to be moist. The limbs are flaccid, and the deep reflexes are absent, while the superficial reflexes remain.

Electrical responses are absent during complete paralysis, gradually returning as the paralysis diminishes.

Physical and neurologic examinations at intervals revealed essentially a normal condition except that the patient is not as strong as one would expect from the size of his muscles.

Clinical examinations and tests were supervised by Dr. R. P. Mackay. Dr. W. F. Petersen directed the laboratory analysis and study of the weather correlations.

The patient was admitted to the hospital on Oct. 29, 1938. He was given a special diet low in potassium—approximately 1.6 Gm. per day. He was kept on this diet for one month with no increase in the number or severity of his attacks. During this period insulin and dextrose tolerance tests gave normal results. The basal metabolic rate was —8 per cent.

From December 6 to Jan. 16, 1939, the patient received the regular ward diet daily. Studies were made of the p_H, the carbon dioxide–combining power and the calcium and potassium of the blood. The p_H varied from 7.35 to 7.55. There was no constant correlation between the p_H and the onset of an attack. The carbon dioxide–combining power varied between 43 and 67 volumes per cent, being moderately but invariably reduced during attacks. Calcium values, likewise, averaged lower during the attacks. The range was rather wide, being from 8.92 to 16.49 mg. per hundred cubic centimeters. Determinations of potassium varied from 7.60 to 39.98 mg., 18 to 20 mg. being considered normal. We did not find a critical level, as reported by Aitkin and his associates, but the values averaged much lower during attacks than during a free period.

Studies of the blood pressure, pulse and respiratory rates and temperature showed that there was a definite association between a rising blood pressure and the onset of an attack.

Most authors have concluded that there must be a disturbance in the neuromuscular mechanism or in the muscle itself. Several have stated that they saw rarefaction and degeneration of the striated fibers, with multiplication of their nuclei, many vacuoles, loss of cross striations and some swelling of the fiber bundles. They have then stated that these changes are of no importance because

of the periodic nature of the disease. Even though these alterations have been seen consistently, the writers have all concluded that they are artefacts rather than the cause of paralysis, since in the latter case the patients should be paralyzed for longer periods. Again, these changes are seen in the intervals between attacks.

Two slides will be demonstrated at the end of the paper.

We decided to try intravenous injections of metrazol, 2 cc. of a 10 per cent solution daily, since this condition has been considered to be a polyglandular disturbance and since metrazol is thought to be a strong sympathetic stimulant. The patient was given eight injections between January 16 and 26. This produced little if any change in the clinical picture, but the values for the carbon dioxide–combining power and the p_H fluctuated less, while those for calcium and potassium had a wider range than before.

Dr. A. Schittenhelm stated that foreign protein therapy raised the potassium level of the blood serum; with this in view, we gave the patient typhoid vaccine intramuscularly on alternate days, starting on January 26 and fininshing on February 11. On the first three treatment days he received 1,000,000,000 units; on the second, 2,000,000,000 units, and on the third, 3,000,000,000 units.

The potassium values tended toward a higher level and smaller fluctuations, but the patient had three attacks during this period.

During the period that the patient was treated in the dispensary he was given benzedrine sulfate; he reported that his attacks were less frequent and less severe. This led us to place him under treatment with benzedrine sulfate, 10 mg. being given at 7 and 11 a. m. He was given this medicament from February 13 to March 1. During this period he had almost daily attacks, which varied from slight paresis to complete paralysis.

Comment.—Mrs. Whitcomb and I wish to call attention to several significant facts. 1. The almost constant onset of attacks in the early morning. This corresponds to a diurnal period of sympathicotonia, when there is a sudden shift from the condition of dilatation of the blood vessels and lowered blood pressure to one in which the vessels contract and the blood pressure increases markedly. At this time, too, most of the potassium ingested in the evening meal has been absorbed from the intestine, and little is available to meet the increased demands of the tissues.

2. The patient's statement that he can often foretell an attack from increased fatigue the evening before. This is probably associated with low blood pressure; the lower the blood pressure before the attack the greater the reactivity in the opposite direction and the greater the probability of a threshold level being reached. The irritability and uncooperative state of the patient at the beginning of the attack, with the headache, again indicate a period of vascular spasm.

3. The almost constant relation to meteorologic alterations, particularly to falling temperature and rising barometric pressure. When the temperature is falling and the barometric pressure is rising a physiologic reorientation is necessary. This adjustment is made through a state of relative sympathicotonia, with constriction of the peripheral vascular system and a rise in blood pressure. In unstable persons, such as those suffering from migraine, urticaria, paroxysmal tachycardia and familial periodic paralysis, this normal adjustment, involving all the chemical and endocrine levels of the blood, is often accentuated and leads to an overbalance in the autonomic reaction; the local tissues (heart, skin and muscle) are not able to accommodate to these exaggerated swings with sufficient rapidity or to a sufficient degree, and local dysfunction occurs. If the adjustments required are too frequent or too severe the person is unable to shift his metabolites to obtain the proper balance, and hence has an attack.

We have formulated two theories of the cause of an attack. The patients are endowed with an unstable constitution, which makes them more labile under the disturbing influence of the environment (this includes all factors that may alter the autonomic status—weather, fatigue, trauma and diet), and in turn is shown

by a wide fluctuation in the metabolites of the blood, more specifically, potassium, calcium and phosphorus. This in turn results in periods of poor nutrition to the muscles, which causes the degenerative changes observed.

Our other theory is that there exists a primary defect in the muscles, which function fairly well as long as the metabolites are kept at a relatively high level but are no longer able to function properly when they drop too low.

DISCUSSION

DR. GEORGE B. HASSIN: I should like to ask whether basal metabolic studies in Dr. Blaurock's case showed any abnormalities. I ask because 1 of my patients who evidently suffered from periodic paralysis recovered after an operation for hyperthyroidism. The patient was 40 years of age. He had attacks of paralysis almost every night; after two hours' sleep, he became entirely helpless in the lower extremities, which were much more affected by paralysis than the upper. He consulted a surgeon, who made a diagnosis of hyperthyroidism and operated on him; the patient recovered. I asked experts on hyperthyroidism if they had seen similar cases, but none had. Another patient whose condition I diagnosed as hysteria also consulted a surgeon and recovered after an operation on the thyroid. A thyroidectomy may do the patient more good than discussions of the weather, provided the metabolic studies have given information of dysfunction of the thyroid.

I did not see the patients more than once, but from inquiries I know that they recovered after operations on the thyroid. No such cases have been reported in the literature, and in only one article has a hint at a possible relation between hyperthyroidism and the paralysis appeared. I should like to emphasize that the condition in my cases was not familial but sporadic. I wonder if it would not be better to designate it as periodic paralysis, as Oppenheim did, instead of periodic family paralysis.

DR. R. P. MACKAY: It was my privilege to observe this patient clinically with Dr. Blaurock when he was carrying out the study. He verified the observations of other workers as to the low potassium content of the blood and its relation to the incidence of the attacks. He also demonstrated that the giving of carbohydrates in large quantities with insulin precipitated attacks. The observations which he made as to the relation between meteorologic phenomena and the attacks are interesting and must be accepted, although many are inclined to be skeptical as to the role played by the weather in neurologic conditions. Apparently, in this case neither an unusually low calcium content of the blood nor the coincidence of a rising barometric pressure and falling temperature was effective in producing attacks when acting alone, but if the two factors were present together the attacks supervened. I am inclined to accept Dr. Blaurock's second theory of the presence of an inherent neuromuscular defect which renders the organism peculiarly susceptible to lowered amounts of potassium in the blood. I do not believe that disorders of the thyroid can be considered important in the production of this disease. For many years thyroid was given with some measure of success in the treatment of these patients. Many patients with family periodic paralysis experienced spontaneous remissions of the disease, and it is possible that recovery following thyroidectomy may represent nothing more than a coincidence.

DR. GEORGE B. HASSIN: Dr. Mackay evidently did not understand what I stated, though I tried to make my remarks clear. The operation was not done at my suggestion, and it was for hyperthyroidism, not hypothyroidism. To give such patients thyroid, as Dr. Mackay mentioned, would be wrong. One patient I know is still well after six years. One cannot consider an interval of six years a remission, especially in a case in which paralysis used to occur almost nightly.

DR. LLOYD H. ZEIGLER: This is an interesting paper. It has been a long time since I have seen a patient with this disorder. My experience has not been unlike that of Dr. Hassin, for in the years gone by I have seen a few patients who had something during the course of hyperthyroidism which reminded one of periodic paralysis. It is well known that during hyperthyroidism the muscles of the lower

extremities, particularly the extensor muscles of the legs at the knees, are reduced in strength. Work has been done on the pathologic alterations of the anterior horn cells of the lumbar portion of the cord in cases of hyperthyroidism.

In a discussion of this subject migraine should not be forgotten. One of my patients came from a family in which there was much migraine, and had it himself. The periodic paralysis seemed at times to be an equivalent of migraine. We have all seen cases in which migraine was associated with the circumscribed motor weakness.

Dr. H. Douglas Singer (*Brain* **24**:257, 1901) discovered the effect of potassium on this disease and reported his observations in England.

This is an interesting condition, the study of which may help one to understand other diseases and abnormal forms of metabolism.

Dr. Victor E. Gonda: Were these tests performed with the strongest galvanic currents, and, if so, was there complete loss of response to electric stimulation? There must be the so-called cadaveric reaction, in which the muscle does not contract either to faradic or to galvanic current, before a diagnosis of family periodic paralysis is made.

Dr. Blaurock did not inject more than 2 cc. of metrazol. Perhaps a convulsive dose would have helped. It would be worth while to try.

Dr. Melvin F. Blaurock: Several articles have been published in which the writer pointed out the occurrence of familial periodic paralysis in persons suffering from thyroid struma. This may have been coincidental or the result of faulty diagnosis. Many types of muscular weakness do occur in cases of hyperthyroidism, and some of these disturbances resemble those found in familial periodic paralysis, but the muscles never entirely lose their electrical excitability.

Dr. Gonda raised the question of an important diagnostic test. In familial periodic paralysis there are periods when the muscle does not respond to electrical stimulation. We used currents of both the galvanic and the faradic type, strong enough to cause great pain and almost to burn the patient; yet there was not the slightest reaction in the muscle.

Dr. H. Douglas Singer (1901) was the first to observe that potassium acetate has a beneficial effect on this disease. He concluded that the effect must be diuretic, a washing out of a body toxin.

Biemont and Daniels (*Brain* **57**:91, 1934) recorded several cases in which familial periodic paralysis progressed to spinal muscular dystrophy. They are the only workers of whom I have read who mentioned changes in the anterior horn cells.

The Medullary Control of Respiration. Drs. R. F. Pitts and H. W. Magoun (by invitation).

In a study of the respiratory responses obtained by stimulation of the brain stem of the cat with the Horsley-Clarke technic, we have noted the striking character and definite localization of two types of response. One of these, a tonically maintained, deep inspiratory apnea, which appears to occur in maximal inspiration, is localized to the ventral reticular formation of the medulla immediately overlying the cephalic four fifths of the inferior olive. The other response, which is a maintained expiratory apnea, in some instances occurring in maximal expiration, is localized to the dorsal reticular formation of the medulla, dorsal and slightly cephalic to and cupping the cephalic end of the inspiratory division of the reticular formation.

We offer the following lines of evidence that these two localized reticular regions constitute, respectively, the inspiratory and the expiratory division of the respiratory center: The respiratory responses are well localized within the region which previous workers have vaguely defined as the respiratory center. Responses are coordinated respiratory acts involving both the thorax and the diaphragm. The responses are probably due to stimulation not of afferent or efferent fiber tracts

but of a neuron field closely interrelated synaptically. They are constant responses, only quantitatively influenced by strength and frequency of stimulation. They are independent of the anesthetic used and may be obtained in unanesthetized animals with electrodes sealed in the skull. Inspiratory apnea may be maintained until the death of the animal, in from three to six minutes. Coordinate respiration may be attained by rhythmic stimulation of these centers.

Additional study has shown that combined weak stimulation of the inspiratory centers in the two halves of the medulla yielded responses greater than the sum of the reactions obtained from either half alone, and with stronger currents maximal inspiration was obtained from one half of the medulla, no added effect resulting from combined stimulation of the other half. Direct spread of current was negligible; some arrangement facilitating the spread of excitation within the center must be present.

Combined stimulation of the inspiratory and the expiratory center revealed that each exerted a reciprocal inhibition on the effects of the other, the inspiratory influence being dominant. With various combinations of stimuli this reciprocal inhibition could be utilized in driving respiration in a number of ways.

Inspiratory cramp, or apneusis, induced by pontile decerebration and blocking the vagus nerves, closely resembles the response to stimulation of the inspiratory center. Stimulation of the inspiratory center during apneusis increased inspiration, and after stimulation the increased amplitude was maintained. After more marked stimulation, however, the inspiratory cramp was abolished and then gradually restored. It is suggested that apneusis represents the activity of the inspiratory center under conditions of release. Apneusis could be broken down into rhythmic respiration by successive stimulation of the expiratory center.

DISCUSSION

DR. PAUL C. BUCY: I am intrigued with the idea of the respiratory driving center in the pons to which Dr. Pitts alluded. I should like to know more about the center: exactly where it is located, what its efferent and afferent connections are and what causes it to discharge in a rhythmic manner.

DR. VICTOR E. GONDA: It is unfortunate, indeed, that the fibers of the extrapyramidal tract, which should be severed by the surgeon when operating for torticollis spasmodica, seem to be intermingled with these respiration-regulating fibers demonstrated by Dr. Pitts and Dr. Magoun. This might easily be the cause of sudden death when the surgeon is performing an operation in this region.

DR. ROBERT PITTS: I should like to have Dr. Magoun answer Dr. Bucy's question. With respect to the importance of chemical control of respiration: We do not wish to minimize this aspect of respiratory regulation. We simply have not been interested in this problem. We have been so occupied in finding out something about the basic neural control of respiration that even the obvious interrelations of neural and chemical control have been neglected. For instance, peripheral as well as central chemical mechanisms are active in respiratory control. These peripheral mechanisms, the carotid and the aortic body, must be brought into neural connection with the centers. Just how or on what portions of the centers they exert their effects has not been determined. Neither have we yet investigated the effects of variation in chemical environment on excitability of these centers. Thus, even in the field of neural respiratory control the number of problems opened up by this investigation exceeds those elucidated by it.

DR. H. W. MAGOUN: Evidence for the pneumotaxic function of pontile levels of the brain stem has been deduced from the inspiratory release, called apneusis, which follows isolation of the respiratory center by low pontile decerebration and blocking the vagus nerves. This striking effect was described by Marckwald as early as 1880, or almost twenty years before the classic release phenomenon of decerebrate rigidity, but apneusis is still almost entirely neglected in most textbooks of physiology, and has even been dismissed by recent workers in the field of respiration as simply a concomitant feature of decerebrate rigidity.

Added work, which Dr. Pitts did not have time to discuss, has shown, however, that those regions of the brain which are concerned in inhibiting the medullary centers responsible for decerebrate rigidity—the motor areas of the cortex, the red nucleus and the paleocerebellum—play no role in preventing apneusis, for these regions may all be removed and the vagus nerves blocked without the appearance of apneusis. The essential neurons are as yet unidentified, but are located at a high pontile level, and uncrossed pathways run back from them through the most lateral part of either side of the upper medulla.

Furthermore, the recent work of Stella and the results which Dr. Pitts has just presented strongly indicate that the activity which is released in apneusis does not proceed from the vestibular nuclei, to which decerebrate rigidity is usually attributed, but arises from the reticular neurons which make up the inspiratory division of the respiratory center.

ENERGY OUTPUT OF PSYCHOTIC PATIENTS AND OF NORMAL PERSONS. DR. S. H. KRAINES.

News and Comment

AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY, INC.

The following physicians were granted diplomas in psychiatry and/or neurology at an examination held in New York, Dec. 17, 1939 (an asterisk denotes complementary certification, a certificate having been granted in the other discipline previously).

Neurology.—Joseph L. Abramson, Brooklyn; Noble R. Chambers,* Syracuse, N. Y.; William Ehrlich, Newark, N. J.; Harold L. Ellis, New York; Abraham Ettleson, Chicago; Malcolm J. Farrell,* Waverley, Mass.; Jacob H. Friedman,* Bronx, N. Y.; Archibald, M. Gaulocher,* Wingdale, N. Y.; William F. Green,* New York; Edgar Erskine Hume, Washington, D. C.; Erwin Jaffe, New York; Erich Liebert,* Elgin, Ill.; J. Grafton Love, Rochester, Minn.; Rupert B. Raney, Los Angeles; Alexander T. Ross, Wahjamega, Mich.; Hawley S. Sanford, Detroit; Nathan, Schlezinger, Philadelphia; Michael Scott, Philadelphia; Joseph H. Siris, Brooklyn; Albert T. Steegmann,* Cleveland; Anthony S. Tornay,* Philadelphia; A. Earl Walker, Chicago; Paul H. Wilcox,* Waltham, Mass.

Psychiatry.—Henry D. Allen Jr., Milledgeville, Ga.; William G. Barrett, Boston; Harold H. Berman, Ogdensburg, N. Y.; Vernon Branham, Woodbourne, N. Y.; Edward L. Brennan, Hartford, Conn.; Walter Briehl, New York; Leonard M. Brown, Northport, N. Y.; Alan Challman, New York; Eric Kent Clarke, Minneapolis; Agnes Conrad, New York; Anna R. Coyne, Washington, D. C.; William C. Davis, Ventnor, N. J.; Daniel C. Dawes, Waverly, Mass.; John L. Donahue, Tucson, Ariz.; Henry H. Drewry, New York; Leonard M. Dub, Columbus, Ohio; Knox H. Finley, Boston; Arthur N. Foxe, New York; Ethel H. Friedman, Allentown, Pa.; William E. Glass, North Grafton, Mass.; Melvin Goodman, Hathorne, Mass.; Royal C. Gray, Minneapolis; Harold B. Hanson, St. Paul; Aleck D. Harrison, Crownsville, Md.; Herbert E. Heim, Harrisburg, Pa.; Maurice A. R. Hennessy, Cleveland; Leonard E. Himler,* Ann Arbor, Mich.; Knut H. Houck, New York; Benjamin Karpman, Washington, D. C.; John E. Lind, Washington, D. C.; Herman S. Major, Kansas City, Mo.; David E. McBroom, Cambridge, Minn.; Marjorie C. Meehan, Princeton, N. J.; Emerson A. North, Cincinnati; Samuel Z. Orgel, New York; John F. Owen, Raleigh, N. C.; Nishan A. Pishayan, Schenectady, N. Y.; Naomi Raskin, Boston; Robert H. Rea, Fort Steilacoom, Wash.; J. Davis Reichard, Lexington, Ky.; Norman D. Render, Worcester, Mass.; N. K. Rickles, Seattle; Sarah M. Saklad, Providence, R. I.; Val B. Satterfield, St. Louis; Robert A. Savitt, Queens Village, N. Y.; William Scholten, Kalamazoo, Mich.; Patricia H. Steen, Kings Park, N. Y.; Reginald R. Steen, New York; Francis J. Tartaglino, Washington, D. C.; John H. Travis, Willard, N Y.; Charles L Trickey, Tewksbury, Mass.; Elizabeth R. Vann, Washington, D. C.; Perry V. Wagley, Pontiac, Mich.; James Watson, Raleigh, N. C.; Clarence L. Whitmire, American Lake, Wash.; Harold W. Williams, Howard, R. I.; Isaac N. Wolfson, Poughkeepsie, N. Y.; Zuleika Yarrell, New York.

Neurology and Psychiatry.—John A. Abbott, Cambridge, Mass; Prince P. Barker, Tuskegee, Ala.; Clarence H. Bellinger, Brooklyn; Morris B. Bender,

New York; Irving Bieber, New York; Douglas G. Campbell, Chicago; William B. Cline III, Wingdale, N. Y.; Bernhard Dattner, New York; John B. Dynes, Boston; Edward J. Engberg, Faribault, Minn.; William H. Everts, New York; Victor E. Gonda, Chicago; Morris Herman, New York; William L. Holt Jr., Worcester, Mass.; William A. Horwitz, New York; Charles A. Koenig, Woodville, Pa.; Karl H. Langenstrass, Washington, D. C.; Irwin Levy, St. Louis; Judah Marmor, New York; Matthew T. Moore, Philadelphia; Frank G. Norbury, Jacksonville, Ill.; Philip B. Reed, Indianapolis; Alice E. Rost, Kingston, N. Y.; Daniel Schneider, New York; Herman Selinsky, New York; Benjamin Simon, Worcester, Mass.; Franklin C. Southworth Jr., Buffalo; Wayne H. Taylor, New York; Carl E. Trapp, Boston; Frederic Wertham, New York; Sidney D. Wilgus, Rockford, Ill.; Benjamin F. Williams, Lincoln, Neb.; Guy H. Williams Jr., Macedonia, Ohio.

Book Reviews

Social Forces in Personality Stunting. By Arnold H. Kamiat. Price, $2.50. Pp. 250. Cambridge, Mass.: Sci.-Art Publishers, 1939.

In this readable, vigorous essay the author seeks to direct attention to what he believes to be an important and long-neglected fact, without which the ills of both the individual and society are not comprehensible. His thesis is that the great majority of the physically adult population of the world of all times has been psychologically—i. e., intellectually, emotionally and volitionally—immature. He includes in this characterization most of the leaders in industry, politics, military affairs and the church. Wherever the organization of human society is characterized by exploitation, autocracy and competition—in which the growth of individuals is considered to be dependent on "spiritual anthropophagy"—the result is arrested and imperfectly integrated personalities in both the exploited and the exploiters, the victims as well as the victors in the conflict. The aim of the predominant activities of such a society—which are industrial, political and military—is megalomanic power over others, and this is largely illusory since in the competition institutions function largely as devices to restrict the influence of every person over others. The characteristic mentality of the individual member of such an organization shows a marked resemblance to paranoia: delusions of infallibility, of messianic predestination; intolerance for all dissentient opinion, with prevalence of the affects of fear and hatred. These are manifested chiefly in the form of group behavior, in which the group may be based on sex, vocation, nationality or religious tenet. The individual member, in regard to the aims of the group, may be said to suffer from the collective paranoia of the group.

As against this human level of social organization, Kamiat pictures one which is primarily democratic and cooperative—in which the growth of the personality requires and in turn fosters the growth of other personalities. The chief activities of such a society would be cultural, i. e., concerned with the creation and appreciation of artistic, scientific, philosophic and ethical values. "The ethical embraces all behavior conducive to the fullest maturation of human beings." The marks of psychologic maturity in members of such a society are a capacity to socialize impulses, to approach problems rationally and objectively, and a predominance of sympathetic and benign affects. The economic, political and ecclesiastic activities, if any, would be assimilated to the ethical and therefore cultural.

With this distinction in mind Kamiat discusses the need for a reinterpretation of history and exclusion of myths about "the great" men and women of the past or present. At some length he elaborates his comparison of immaturity and paranoia, attempts to establish intolerance as an important indication of immaturity, points out the vicious circle of the immature parents rearing none but children who cannot become mature, and exposes the inferiority of ruling groups and their power as illusory. The dictator is at bottom slavish and the slave dictatorial. The role of masochism and sadism in the relations between the sexes, with their accompanying feminist and masculinist delusions of superiority of gynarchic and androcratic societies, respectively, and the mutually stunting influence of these attitudes on both sexes are also considered. Finally, a program is offered which includes, among other plans, democratization of all human activity; transformation of government into a collaboration between trained statesmen and administrators, on the one hand, and scientists (especially of the social and biologic fields) and technologists, on the other; socialization of instruments of production and distribution; establishment of freedom of thought, and compulsory education

for all up to termination of the college course. This is not a panacea, but an attempt to introduce the scientific, self critical, experimental attitude into all phases of human activity. A hypothesis is a sufficient guide for action in socio-economic and political affairs, as well as in science.

Clinical and Experimental Studies in Personality. By Morton Prince. Revised by A. A. Roback, PH.D. Price, $6. Pp. 670. Cambridge, Mass.: Sci-Art Publishers, 1939.

This fine volume is a revised and enlarged reprinting of the book which appeared in 1929. The old edition being exhausted and the demand still continuing, Dr. Roback is to be congratulated for having accepted and ably completed the task of revision. His preface and essay on "Prince's Place in Psychology" make an excellent introduction.

It is now ten years since the death of Dr. Prince, and the psychology of personality which he helped so much in creating is taking an important place. Janet, Freud and Jung were largely clinical in their approach; Prince always had a flare for the experimental, and this adds greatly to the data which support his discussions. By giving the best of Prince's work this book becomes a fundamental text for both clinicians and investigators in the field of abnormal psychology. The chapter on "The Role of Meaning in the Psychoneurosis," though not a deep analysis in the freudian sense, shows that in 1912 Prince was far ahead of his time in comprehending the importance of subconscious motives. In fact, his description of subconscious and conscious phenomena is more exact than the unreal, dualistic division of everything into conscious or unconscious of more recent psychoanalysts. The chapter on "Association Neurosis," modified from the original paper of 1891, shows Prince as a pioneer in the field of "conditioned reflexes."

Hypnosis is an important tool for the investigators of personality. It used to be important in therapy, and in fact may be more important than one realizes, for Prince gives good evidence (chapter 5) that what one usually calls hypnosis is an artificial narrowing of the field of consciousness associated with depersonalization and repersonalization. States of abstraction, revery, absent-mindedness, trances and fugues are the same sort of phenomena. The state of abstraction induced by lying on the couch during psychoanalytic free association may be an important element in the therapeutic repersonalization. At least, a modern psychologist cannot afford to disregard all that is known about hypnosis, and many of them are not only ignorant but scornful of the subject. Prince does not say what hypnosis is; he calls it a riddle; but at least he logically reduces it to component phenomena which one can better understand: inhibition, dissociation, depersonalization and repersonalization.

The other chapters, on such problems as consciousness, dreams and hallucinations, show the same keen, logical mind willing to use in a catholic way data from academic physiologists, psychologists, neurologists and psychiatrists. Prince was at times polemic, but he rode no hobby and founded no school. His work had little popular acclaim during his life, but this book will be read by serious students when the contemporary mass of glib psychiatric speculation is gathering dust on the back shelves.

Theories of Sensation. By A. F. Rawdon-Smith. Price $2.75. Pp. 119, with 18 illustrations. New York: The Macmillan Company, 1939.

This little volume is devoted primarily to a brief summary of the literature regarding the function of the peripheral receptors of vision and audition. The first half of the volume deals with a discussion of the formation of the retinal image, the evidence for the duality of the retinal process and color vision. Some of the difficulties in the attempts to explain visual acuity and intensity discrimination solely in terms of photochemical changes are pointed out, and the inadequacies

of the Weber-Fechner fraction are considered. The importance of a few of the early studies on the electrophysiology of the retina is emphasized. The second half of the volume contains a summary of the peripheral auditory process, and is divided into short chapters on the anatomy of the ear, the perception of pitch and theories of the perception of loudness. These chapters are well written and summarize clearly the evidence for the relationship of pitch, loudness and nerve impulses.

This book may be recommended to those who are interested in a brief introduction to some of the problems and difficulties which arise when attempts are made to explain vision and audition solely in terms of the mechanisms of the peripheral receptors. While the volume is entitled "Theories of Sensation," the author considers only the peripheral receptors; possible function of cerebral mechanisms is not mentioned. Actually, the volume is a brief introduction to a study of the available evidence relating to the mechanisms whereby the peripheral receptors of vision and audition react to their specific physical stimuli.

Notices

CUMULATED INDEX OF THE ARCHIVES OF NEUROLOGY AND PSYCHIATRY

Requests have been received for a twenty year index of the ARCHIVES OF NEUROLOGY AND PSYCHIATRY. Before serious consideration is given to the production of a cumulated index, it is desirable to know whether the demand for it would be sufficient to warrant its sale at not to exceed $6 per copy; that is, whether one thousand copies could be sold. It will be appreciated if those who are interested in such an index will fill out and send the form which appears below to the Managing Editor at the publication office, 535 North Dearborn Street, Chicago.

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